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CLINICAL AND EXPERIMENTAL

EXSANGUINATION-TRANSFUSION IN TREATMENT OF PHENOL POISONING*

BY CHAS. C. HASKELL, R. C. ALLEY, AND P. E. PRILLAMAN
RICHMOND, VA.

POISONING by phenol and the closely related cresols is still of such frequent occurrence as to render a knowledge of appropriate therapy most essential. When the poison has been taken orally, gastric lavage is the most important measure to be employed, this being well illustrated by the statisties of Clarke and Brown.[1] These authors show that recovery almost invariably occurred when gastric lavage was practiced early; even after doses as large as two ounces of liquefied phenol, an amount over five times the estimated average fatal dose for man. Unfortunately, however, considerable time may elapse before the patient is seen by anyone familiar with the relatively simple technic of gastric lavage. It would be most desirable, therefore, to secure a substance which is capable of detoxicating the phenol, either in the stomach or after it has been absorbed.

Of the various antidotes which have been proposed for phenol, none has proved satisfactory. Some fifty years ago, Baumann[2] noted that phenol was excreted in the urine partly in the form of ethereal sulphates; from this observation, the sulphates were suggested as phenol antidotes. As with the case of many other therapeutic measures whose only virtue is their novelty, the sulphates were employed by certain investigators with apparent success in the treatment of phenol poisoning; it was demonstrated by Tauber,[2] and especially by Sollmann and Brown,[3] that neither sulphates nor sulphites exercised any practical influence on the course of experimental phenol poisoning.

Apparently, Seneca Powell was the first to suggest ethyl alcohol as an antidote for phenol.[1] It was contended that the alcohol combined chemically

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From Department of Pharmacology, Medical College of Virginia.

with the phenol, thus detoxicating the poison. Gross explained the mechanism involved as consisting in the formation of "a new phenol benzine or aromatic compound" with the properties of ethyl alcohol. As in the case of the sulphates, this antidote, likewise, was used with apparent success in clinical poisoning by phenol, the observers disregarding the fact that gastric lavage was employed coincidentally in practically every case. In 1906, Clarke and Brown[1] reviewed the literature on clinical poisoning by phenol and carried out animal experiments, confirming the view that there was no chemical reaction between alcohol and phenol and demonstrating that alcohol possessed little superiority over plain water in gastric lavage.

Impressed, apparently, by the fact that a mixture of camphor and phenol is comparatively nonirritant, Wilson[4] suggested that camphor was a valuable antidote for phenol. While camphor may serve to lessen the intensity of the local action of phenol, the two drugs have a central action not very dissimilar; consequently, it is not surprising to learn that Bond and Haag[5] found camphor definitely to increase the toxicity of phenol.

The valuelessness of these supposed antidotes gives added interest to the paper of Robertson,[6] in which is described a method for the treatment of various forms of systemic intoxication. Though primarily designed for combating the intoxication associated with severe burns, erysipelas, or acute intestinal disturbances in children, the author states that the application of this principle has been followed by success in cases of poisoning by carbon monoxide and by resorcin. Robertson terms his procedure "exsanguination-transfusion"; and states that it consists in the withdrawal of a large amount of blood and the introduction of an equivalent amount (or slightly more) from a healthy donor. In order to prevent collapse on the part of the patient as a result of the severe blood loss, the procedure is carried out by withdrawing only small quantities of blood at a time, and replacing this by the donor's blood, repeating as often as necessary.

A similar procedure was suggested in 1916 by Burmeister[7] for the treatment of mercuric chloride poisoning. Burmeister removed moderate quantities of blood from the jugular vein of poisoned dogs and immediately injected a suspension of washed corpuscles. He was unable to save any of the treated dogs, but states that the intensity of the renal damage was less in these than in the controls. The use of Robertson's technic in the treatment of dogs poisoned by the intravenous injection of a just fatal dose of mercuric chloride has likewise proved incapable of preventing a fatal outcome in our experience[8]; nevertheless, because of the favorable report of Graham and Tisdall[9] on the use of transfusion or of bleeding and transfusion in the treatment of resorcin poisoning, it was felt that the value of the procedure in phenol poisoning should be made the subject of investigation.

Bond and Haag[5] place the fatal oral dose of liquefied phenol for dogs at about 0.4 c.c. per kilogram body weight. Since they administered this amount to only three dogs, it was determined to run a larger series of animals in confirmation of their results.

The dogs used in our experiments were full-grown, apparently healthy adults. They were fasted twenty-four hours, but were allowed free access

to water at all times. Morphine sulphate, 20 mg. per kilogram, was injected subcutaneously; and, in about thirty minutes, the phenol was given through a stomach tube. Undiluted liquefied phenol was employed; this was measured from a burette into a small funnel connected with the stomach tube and was followed by from 50 to 150 c.c. of wash water. The results of these experiments are given in Table I.

TABLE I

RESULTS OF ORAL ADMINISTRATION OF PHENOL TO DOGS

DATE	WEIGHT IN KG.	MORPHINE MG. × KG.	PHENOL C.C. × KG.	RESULT
3-26-25	7.7	20	0.3	Died in 3 days.
3-30-25	4.7	20	0.3	Recovered.
4- 3-25	14.0	20	0.3	Recovered.
4- 4-25	19.4	20	0.3	Died in 2 days.
4- 6-25	10.6	20	0.4	Died in 2 days.
4- 7-25	6.5	20	0.4	Died in 24 hours.
4-10-25	11.5	20	0.4	Died in 2 days.
4-15-25	9.9	20	0.4	Died in 6 days.
5- 4-26	15.0	20	0.4	Died in 24 hours.
5- 4-26	15.0	20	0.4	Died in 2 days.
5- 4-26	15.7	20	0.4	Died in 24 hours.
5- 4-26	13.4	20	0.4	Died in 24 hours.
5- 4-26	11.9	20	0.4	Died in 5 days.
5- 4-26	11.6	20	0.4	Died in 24 hours.

From these results, it was assumed that the fatal dose of liquefied phenol administered to dogs in the manner described lay between 0.3 and 0.4 c.c. per kilogram body weight.

The dogs treated by exsanguination-transfusion were first given morphine sulphate, subcutaneously, 20 mg. per kilogram, and then the liquefied phenol orally. Within a few minutes, the characteristic action of the phenol became manifest, the animals losing consciousness and developing coarse, convulsive twitching of the striated muscles. After varying lapses of time, the femoral vessels were exposed, the depression of the central nervous system by the phenol being so great as to render the use of any other anesthetic unnecessary. Blood was withdrawn from the artery in an amount varying with the weight of the dogs, and this was followed immediately by injection of a slightly greater amount of citrated blood from an apparently healthy donor into the femoral vein. The blood of the donor had previously been matched with that of the recipient. Only three animals were treated in this way; the results were so uniformly unfavorable as to discourage further efforts along this line. These results are given in Table II. Here, as in the remaining tables, when an animal died during the night subsequent to administration of the phenol, its death was said to have occurred "in twenty-four hours." In many, indeed, most, instances, the duration of life was considerably less than twenty-four hours; in view of our ignorance of the exact time of death, the rule mentioned was arbitrarily adopted.

Reference to Table I shows that of four control dogs given the oral dose of 0.3 c.c. liquefied phenol per kilogram body weight, two recovered without treatment. Both the animals that received this dose and were treated by exsanguination-transfusion not only succumbed but death occurred much

TABLE II

RESULTS OF EXSANGUINATION-TRANSFUSION TREATMENT OF PHENOL POISONING

WT. IN KG.	PHENOL C.C. × KG.	TIME	BLOOD DRAWN	TIME	BLOOD INJECTED	TIME	RESULT
5.0	0.3	5.10	150 c.c.	5.42	175 c.c.	5.53	Death 15 min.
3.5	0.3	5.35	100 c.c.	6.12	150 c.c.	6.25	Death 3 min.
5.8	0.4	3.35	175 c.c.	4.20	145 c.c.	4.30	Death 24 hrs.

more promptly than in the case of any of the control dogs. Strangely, the dog that was given 0.4 c.c. of phenol and then treated by exsanguination-transfusion lived longer than either of the animals receiving the smaller dose of phenol. It is to be noted that this dog received less blood than was removed from its vessels.

Similar unfavorable results were observed in a larger series of animals given barely fatal doses of mercuric chloride intravenously and then subjected to the exsanguination-transfusion therapy.[8] In these animals, the technic of Robertson was strictly adhered to: relatively small amounts of blood were withdrawn repeatedly, to be promptly replaced by injections of blood from the donor. Although the bloods of the donor and recipient were roughly matched before the administration of the phenol, the suspicion arose, naturally, that either the bleeding or the subsequent injection of the citrated blood was responsible for the unfavorable results. In order to determine the influence of the bleeding alone, a series of nine dogs was used. These animals were given morphine and varying doses of phenol, the procedure being similar to that used in the previously described experiments. In from twenty-three to seventy minutes, the dogs were bled from the femoral artery and then given intravenous injections of isotonic salt solution, the volume of the latter being slightly greater than that of the blood withdrawn. The outcome of these experiments is given in Table III.

TABLE III

RESULTS OF EXSANGUINATION AND SALINE TRANSFUSION TREATMENT OF PHENOL POISONING

WT. IN KG.	PHENOL C.C. × KG.	TIME	C.C. BLOOD DRAWN	TIME	C.C. SALINE INJECTED	TIME	RESULT
15.4	0.3	3.26	470	4.10	500	4.20	Recovery.
12.5	0.4	4.31	375	5.10	435	5.20	Recovery.
11.7	0.4	3.45	351	4.55	400	5.00	Recovery.
10.0	0.4	3.40	300	4.18	350	4.30	Death 24 hours.
12.0	0.4	4.58	360	5.30	420	5.38	Death 24 hours.
8.9	0.4	4.10	280	4.45	320	4.55	Death 24 hours.
15.9	0.4	12.02	500	12.25	600	12.31	Death 24 hours.
13.4	0.4	12.34	400	1.38	600	1.39	Death 6 hours.
15.6	0.4	12.39	470	1.02	650	1.12	Death 24 hours.

The fact that two of the dogs that were given the dose of 0.4 c.c. of liquefied phenol per kilogram body weight recovered after bleeding and saline injection would appear to indicate that this procedure possesses some merit in the treatment of phenol poisoning. Opposed to this, however, it is apparent that death occurred more quickly in the fatal cases of this series than in the series of control dogs; the average duration of life after adminis-

tration of phenol in the former being less than twenty-four hours; in the latter, about two days. It is certainly safe to conclude, however, that withdrawing large amounts of blood and subsequently injecting isotonic saline has no such detrimental effect as seen when the bleeding was followed by the injection of citrated blood.

In spite of the fact, previously mentioned, that the bloods of donor and recipient were roughly matched before transfusion, the conclusion could scarcely be escaped that the unfavorable results were connected with the injection of the blood. The next step, therefore, was to determine the effect of exsanguination-transfusion on unpoisoned dogs. In order to do this, seven dogs were used. The animals were given 20 mg. of morphine sulphate per kilogram subcutaneously; and, under ether anesthesia, the femoral vessels were exposed. Amounts of blood equivalent to from 3 to 5 per cent of the body weight were withdrawn from the artery; and this was followed immediately by the injection of citrated blood into the vein. In two cases, the operative wound became badly infected; the dogs succumbing, apparently to this infection, on the fourth and seventh days respectively. A third dog seemed to be doing well but suffered a fatal hemorrhage on the fifth day. The remaining dogs seemed uninjured by the procedure, and were apparently normal in from eight to eleven days, when they were used for other purposes.

CONCLUSIONS

The following conclusions seem justified:

1. The minimal fatal dose of liquefied phenol by oral administration to dogs that have been previously fasted twenty-four hours and given morphine to prevent emesis is in the neighborhood of 0.3 to 0.4 c.c. per kilogram body weight.

2. The withdrawal of large amounts of blood and the subsequent injection of presumably combatible citrated blood exerts a definitely unfavorable influence in poisoning by phenol. The reason for this is obscure.

3. The withdrawal of large amounts of blood and the subsequent injection of isotonic saline may be of some benefit in the treatment of phenol poisoning; if the procedure is of any value, it is slight.

4. Exsanguination-transfusion, except in so far as it may offer a portal of entry for infection or give rise to the possibility of hemorrhage, appears to be a safe procedure for unpoisoned dogs.

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A CONTRIBUTION TO THE NATURE OF DIABETES*
A MATHEMATICAL DERIVATION OF THE BLOOD-GLUCOSE CURVE

BY DWIGHT M. ERVIN, M.D., SAN FRANCISCO, CALIF.

IN A previous article it was stated that failure of the oxidation of glucose could not be the basis of the condition of diabetes.[1] This belief has led to the mathematical construction of the blood-glucose curve in order to see what effect the failure to oxidize glucose would have upon the normal curve.

The glucose tolerance curve as generally given is a curve resulting from the rate that glucose is absorbed from the intestinal tract; the rate the glucose is converted into glycogen, and the rate that the glucose is oxidized from that absorbed. There is a definite mathematical rate that glucose will be absorbed from the intestinal tract from a given concentration. Likewise the rate that glucose will be converted into glycogen depends upon the concentration of the glucose in the blood stream. The rate of oxidation, however, is independent of both the intestinal tract and blood concentrations.

When once the blood-glucose tolerance curve is obtained in mathematical form it is possible to investigate each rate individually and its effect upon the curve when the rate is altered. If we choose to investigate the effect of oxidation upon the curve we may do so by changing the rate of the oxidation as is presumably done in the diabetic. We may even decrease the rate of oxidation to zero, making a complete diabetic, and investigate the effect of this zero oxidation upon the curve.

As glucose is absorbed from the intestinal tract its rate at any point of time in the entire length of time of the absorption is dependent upon the concentration of glucose in the intestinal tract at that point of time. But this concentration is always decreasing by the amount absorbed.

Let a = initial concentration.

x = quantity absorbed.

$\frac{dx}{dt}$ = rate of absorption.

(1) $$\frac{dx}{dt} = k_1 (a-x)$$

k_1 = constant of absorption.

$\frac{do}{dt}$ = rate of oxidation which is constant.

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(2) $\frac{do}{dt} = c$

c = constant of oxidation.

Integration of equation one gives—

$a - ae^{-k_1 t}$ = x quantity absorbed.

integration of 2.

(3) $o = ct$ quantity oxidized at any given time.

Hence the quantity in the blood stream at any given time if glycogen formation does not take place is the quantity absorbed less the quantity oxidized.

(4) $a - ae^{-k_1 t} - ct$ = the blood stream concentration.

As the glucose is absorbed the conversion into glycogen takes place and the rate that it does so will depend upon the glucose passing into the blood stream less the quantity converted into glycogen and oxidized at any point of time.

(5) $\frac{dz}{dt} = k_2 y$

where y = the quantity in the blood stream

k_2 = constant of glycogen formation.

(6) $\frac{dy}{dt} = \frac{dx}{dt} - \frac{dz}{dt} - \frac{do}{dt}$

Substituting the values for $\frac{dx}{dt}$; $\frac{dz}{dt}$; and $\frac{do}{dt}$ and integrating the equation we derive the value of the quantity of glucose in the blood at any point of time.

(7) $$y = \frac{k_1 a e^{-k_1 t}}{k_2 - k_1} - \frac{k_1 a e^{-k_2 t}}{k_2 - k_1} - cte^{-k_2 t}$$

The test of this equation must be that, as k_2 (or the rate of glycogen formation) becomes zero, the equation must equal the amount absorbed less the amount oxidized

making $k_2 = 0$

7 becomes $y = a - ae^{-k_1 t} - ct$ = equation 4 or $x - ct$

In this equation the rate of oxidation is independent of the concentration in the blood stream. This is not strictly true for Lusk found the specific dynamic action for glucose to be about 10 per cent. For this purpose the increase of oxidation is very small and will not affect the curve within the limits of practical errors.

There are to this equation of glucose in the blood stream three constants, k_1, k_2, and c; k_1 determines the rate of absorption, k_2 the rate of glycogen formation, and c the rate of oxidation.

The values of k_1, k_2, and c may be determined as follows: For any given case that is normal we may obtain two important points. The crest of the

blood-sugar curve and the quantity in the blood at an interval of three hours. To an individual of 70 kilos weight, 95 gm. of glucose were given in one liter of water. At 0.7 hours the crest of the curve was reached and at 3.0 hours the curve had returned to 30 mg. above normal.

Seventy kilos weight gives closely 5 kilos of blood. When 100 mg. are present per 100 c.c. of blood there is a total of 5 gm. When 35 mg. are present there is a total of 1.7 gm.

At the crest of the curve the tangent to the curve is equal to zero.

$$(8)\quad \frac{dy}{dt} = 0 \quad (t - 0.7)$$

Differentiating 7 $k_2 = nk$. and setting it equal to zero we have

$$(9)\quad 0 = -\frac{k_1 a e^{-k_1 t}}{n-1} + \frac{k_1 a e^{-k_2 t}}{n-1} - (c - c t k_2)\, e^{-k_2 t}$$

At t equal 0.7 the blood glucose has risen from 100 mg. at the beginning of the test to 200 mg. This is equal to an increase of 5 gm.

Substituting $a e^{-k_2 t}$ from 7 $(t - 0.7;\ y = 5)$ and solving for n we get

$n = 1$ or 13

$k_2 = 1k$, or $13k$,

again from 7 $(t - 3;\ b - 1.7)$

$k_1 = 0.38$

$k_2 = 4.94$

The computation of c is much simpler. From the basal metabolism at the respiratory quotient of 0.84 we find 45.6 per cent of the calories are derived from glucose.

Height 70 inches.

Weight 70 kilos.

Total surface 1.78 square meters.

Total metabolism per hour 71.2 calories.

Calories derived from glucose per hour 32.4.

Grams of glucose burned per hour 8.0.

Constant c = 8.0.

In Chart I, Curve 1 is the blood curve from which the equation was derived. Curve 2 is the curve of the derived equation.

With the equation of the curve developed we can investigate each of its parts that enter into its structure. If we desire to find how the normal curve would be altered when we decrease the rate of oxidation in the body we have but to decrease the value of the constant c.

Let c be made zero in equation 4 and the equation now becomes—

$$y = \frac{k_1 a e^{-k_1 t}}{k_2 - k_1} - \frac{k_1 a e^{-k_2 t}}{k_2 - k_1}$$ the equation of a complete diabetic.

If this curve is now plotted as the curve that a diabetic would develop if he did not oxidize sugar—a complete diabetic—we find it even in the most

exaggerated form to differ only in the smallest degree from the normal. From a mathematical point of view, if we grant that absorption and glycogen formation are consecutive simultaneous reactions, it is impossible for the failure of oxidation to produce the curve that is found in the diabetic. *If the diabetic does not burn glucose it is a fact unrelated to his blood-glucose curve*

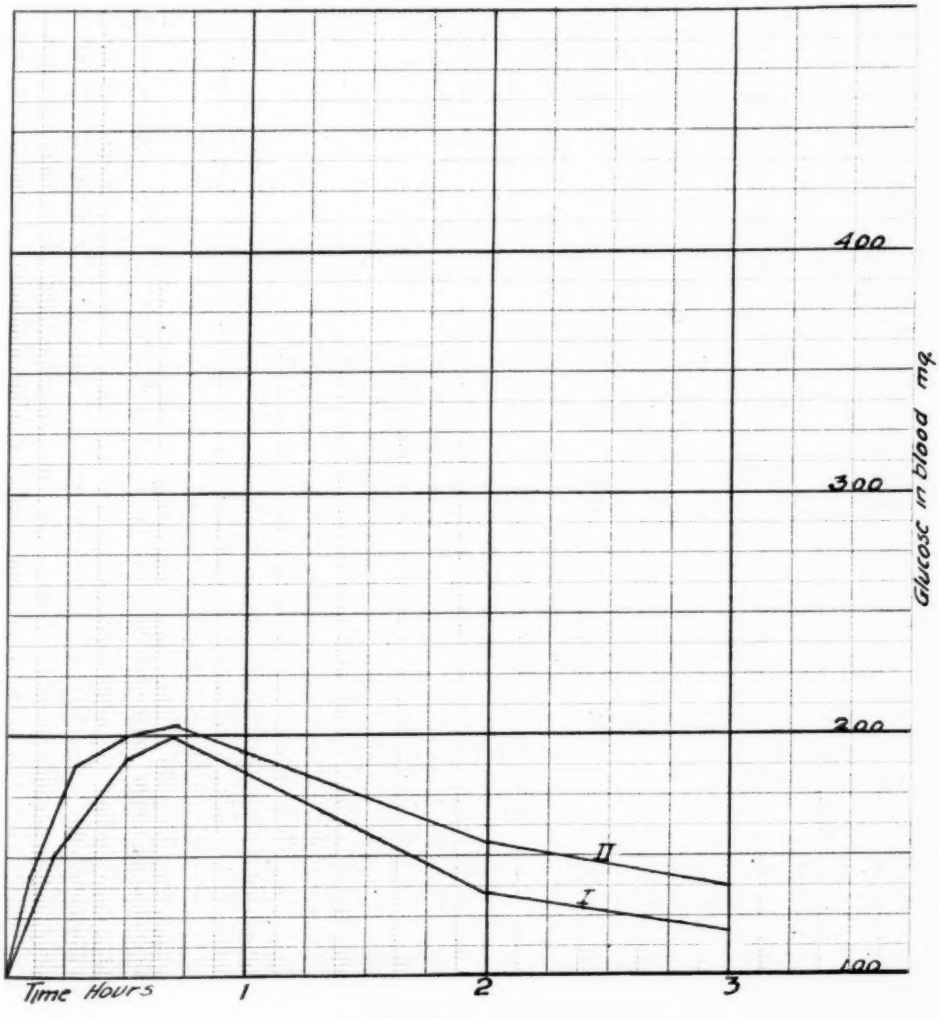

CHART I

and nothing concerning this failure to burn glucose can be derived from the blood-glucose curve. Chart II, Curve 1, normal, Curve 2, oxidation = zero.

We may investigate the remaining constants or rates of reactions, absorptions and glycogen formation. k_1 or the constant of absorption is not likely the cause of the running of glucose in the urine. If it should be the cause it would have to be tremendously increased in value to cause the diabetic curve.

The constant of the rate of glycogen formation, or k_2, may next be altered and the effect upon the curve of a decreased rate of glycogen formation be found. If we make the rate of glycogen formation equal to zero, equation 4 becomes—

$y = a - ae^{-k_1 t} - ct$ or the quantity of glucose absorbed less the quantity burned. Chart III is a comparison of $k_2 = 0$ or a complete diabetic if diabetes is the failure to, or decrease in rate of the formation of glycogen. Since if the blood volume is 5 liters and the glucose is given in one liter of water diffusion would take place until $\frac{4}{5}a$ had diffused. The quantity $ae^{-k_1 t}$ is the quantity of glucose left in the intestinal tract. The value of y would cease to rise when $ae^{-k_1 t} - \frac{4}{5}a$ or $y = \frac{4}{5}a - \frac{4}{5}ae^{-k_1 t} - ct$.

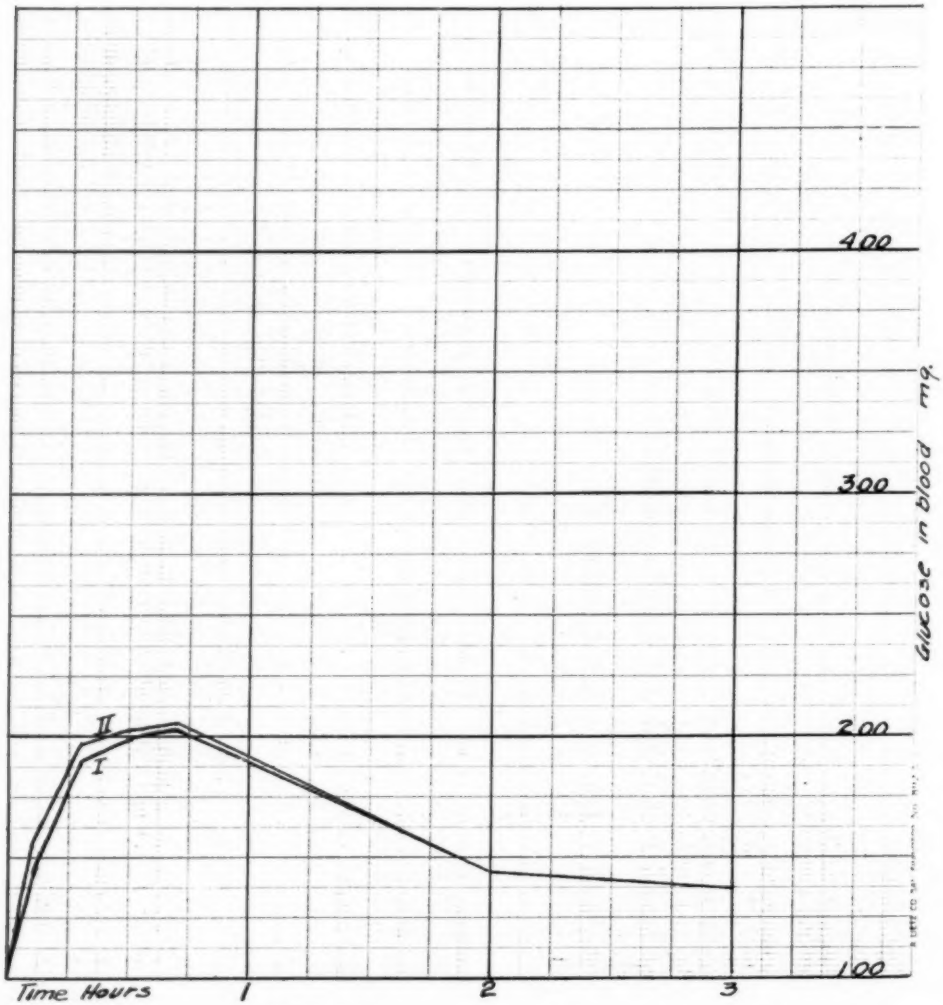

CHART II c=0 Curve II curve I =normal

Chart III includes this correction for the quantity of glucose that diffuses. The alteration of k_2 changes the normal into a curve that approaches that of the diabetic; the sharper rise, the greater height, the delayed, longer, flatter crest, and the slower decline to the normal. We may give k_2 any value we choose between k_2 = normal (4.94) and $k_2 = 0$.

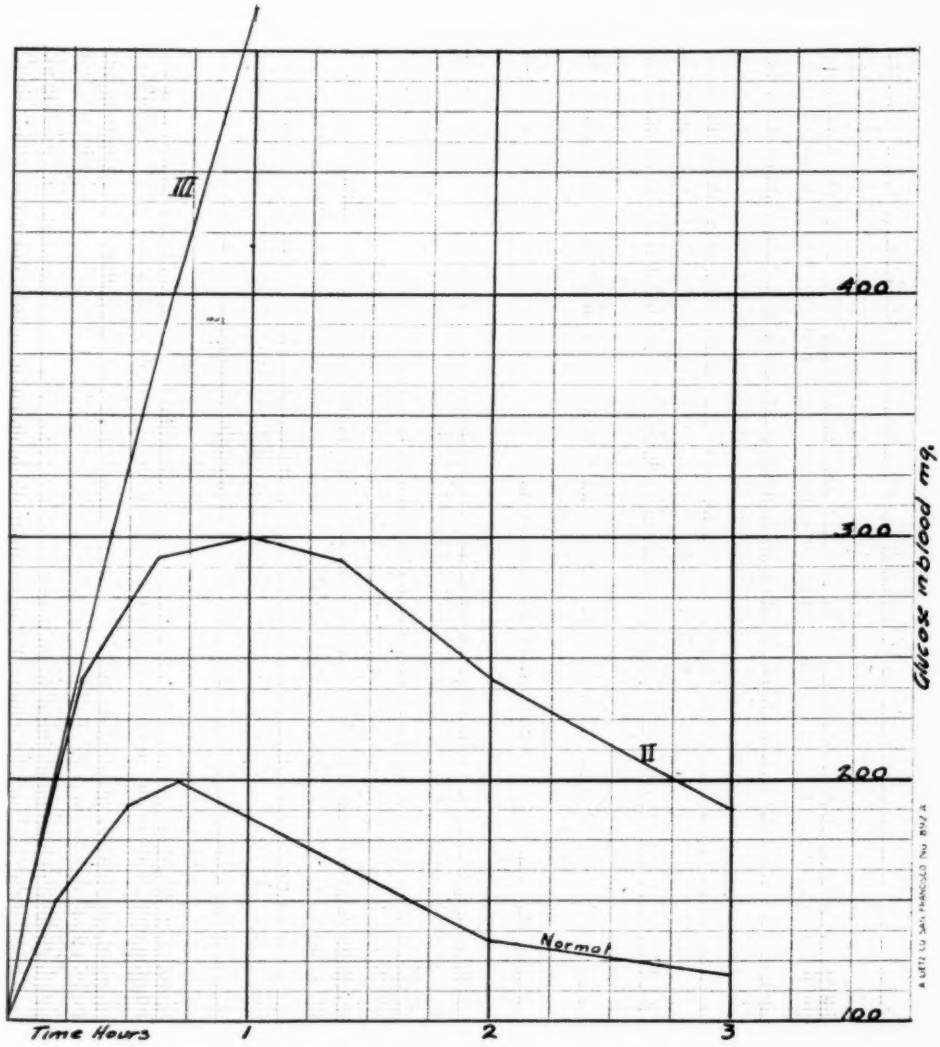

CHART III curve II - $k'_2 = \frac{1}{2}$ normal curve III - $k_2 = 0$

Chart III gives the curve when the rate of glycogen formation is one-half the normal $k_2 = 2.60$. Such a curve is typical of what we find in the diabetic, and is only different in that above the kidney level the curve is altered by the rate of kidney secretion. Such a curve including with this curve the rate of kidney secretion will be published in a future paper.

The slope of the rise, the height of the crest, the sharpness of the crest,

the early or late crest are all dependent upon the values and ratio of k_1 and k_2.

If the ratio $\frac{k_1}{k_2}$ or $k_2 = nk_1$ is kept constant the crest may be made earlier or later by decreasing or increasing the values of both. Hence an early or late crest without the height being considered has no value in the interpretation of a curve. No single feature of the curve taken by itself will give a satisfactory interpretation. All should be considered. The only single feature of the curve that yields a knowledge of what is going on in the curve is the ratio $\frac{k_1}{k_2}$ and an idea of this may be gained from the rate of change of the tangent.

If we inspect the curve of the normal at 0.7 hour we find the tangent at this point parallel to the time ordinate; but in Curve 3 of the diabetic the tangent at 0.7 hour has not yet become parallel to the time ordinate. The rate of change of the tangent is indicative of the ratio $\frac{k_1}{k_2}$

The tangent at any point on the curve is equal.

$$\text{Tan} = \frac{dy}{dt}$$

$$\text{Tan} = -\frac{k_1 a e^{-k_1 t}}{n-1} + \frac{k_2 n e^{-k_2 t}}{n-1} - (c - ctk_2)\, e^{-k_2 t}$$

Hence Tan (t–.2) – Tan (–3) is greater in the normal than in the diabetic. Above the kidney level the values of the curve are misleading.

Since the crest of the curve of a normal is close to 0.7 hour and the diabetic of $\frac{k_2}{2}$ crosses the kidney level at about 0.2 hours there is in the glucose curve a very small range in which we may work.

For this reason a starch curve where k_1 is decreased by the delayed absorption due to the digestion is far better for interpretation of the degree of diabetes. k_1 for 2.0 gm. of starch per kilo weight is at present being determined for the normal.

In the attempt to test our old work[1] by the mathematical equation of the blood-glucose curve we find ourselves back to old position upon the nature of diabetes. The failure to burn glucose can have nothing to do with the presence of glucose in the urine. The glucose curve and the glucose in the urine are not factors of oxidation but of the velocity of glycogen formation or the constant k_2. This leaves only the problem of the "acetone bodies" to the theory of oxidation or failure to oxidize in diabetes; and work in preparation now shows that the formation of the acetone bodies may be accounted for independent of the oxidation of glucose.

As more cases are worked the values of k_1 and k_2 may be determined over a wider range of normals. From this curve the so-called adrenal and thyroid effects can be unravelled by determining which constant, if any, is affected.

SUMMARY

A mathematical equation for the blood-glucose curve of the blood is derived from the three factors, absorption from the intestinal tract, formation of glycogen, and oxidation.

The constants of the curve determining the rate that absorption, glycogen formation, and oxidation goes on are determined.

From these constants the effect on each function on the curve can be investigated.

By placing the constant $c = 0$ we make the rate of oxidation equal to zero—or if diabetes has to do with the burning of glucose—we make a complete diabetes.

The curve derived from failure to burn glucose differs only insignificantly from the normal and in no way approaches the curve found in diabetes.

By investigating mathematically the condition of diabetes from the blood-glucose curve no evidence of the failure to burn glucose can be obtained. But rather that the curve depends only upon a decreased rate of glycogen formation.

REFERENCE

[1]Ervin, D. M.: Jour. Lab. and Clin. Med., 1919, v.

ISOPROPYL ALCOHOL—AN INVESTIGATION OF ITS PHYSIOLOGIC PROPERTIES*

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THE investigations herein reported were instituted in 1921 and comprised a study of the effect on the animal economy of isopropyl alcohol (isopropanol) administered in such dilutions that the acute or local action on the membranes and tissues would be negligible. In other words, it was desired to obtain data on the general systemic action of the substance.

Coincident with the physiologic investigation on animals a series of tests was performed to determine the effect of isopropyl alcohol on bacteria, yeasts and molds in comparison with ethyl alcohol.

PHYSIOLOGIC ACTION

The work included not only a study of the effects of isopropanol on the animal economy, but a comparison of its physiologic action with that of ethyl or grain alcohol, and its effect on bacteria and molds. Its action on the animal economy was determined by observing the effects of its administration to living animals and human subjects. The animals employed included rabbits, dogs, cats, guinea pigs, chickens and a monkey.

In order to give some idea of the way the work was performed the investigation will be briefly outlined.

Subjects.—As noted above, the subjects selected included rabbits, guinea pigs, dogs, cats, chickens, monkeys and humans. Careful attention was given to their health and none but sound vigorous adult specimens were employed. The rabbits were large gray specimens of the Belgian hare type, averaging in weight about four pounds. The animals were kept in a large airy room under normal temperature conditions and were plentifully supplied with water and good wholesome food. The cages were kept in as sanitary a condition as possible, one attendant devoting a considerable part of his time to keeping them clean and attending to the wants of the occupants.

Observations on Living Animals.—Each animal was kept under observation for a period of a week of two before submitting it to the tests. In this way it became possible to observe the normal behavior of the animal, its preferences as regards food and its individual eccentricities if it possessed any.

Careful observations of its daily fluctuations in weight were recorded, the character and frequency of its eliminations, and its general deportment, nervousness, reaction to human contact, etc.

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At the end of its probationary period, it was given a clinical card and admitted to the list of animals receiving the test material.

While under treatment a careful record was kept of its weight, desire for food, condition of its pelage or plumage, and all symptoms of a pathologic nature due directly to the substance administered.

The observations and method of handling the human subjects will be described later.

Observations After Death.—Several animals died during the course of the investigation through accident or through contraction of disease (usually pneumonia). In nearly all cases those which came through the tests alive were killed, though in certain exceptional instances, animals were allowed to survive for a considerable period after the conclusion of the tests in order that special observations might be recorded. These were subsequently killed. In every instance, no matter how the animal came by its death, it was autopsied, the gross pathology noted and then the various organs were immersed in formaldehyde solution. These specimens were preserved in separate jars, numbered to correspond with the clinical card of the subject, and later sectioned and examined microscopically to determine the pathologic conditions.

Technic.—The isopropanol was mixed with an equal volume of water for administration. Doses of not less than 5 c.c. nor more than 20 c.c. were given. Ingestion was effected by introducing a soft catheter through the mouth into the stomach of the animal, and then gently forcing the liquid through the tube by means of a syringe attached to the open end. The syringe was of glass, with a graduated barrel. After receiving the dose the catheter was withdrawn and the animal returned to its cage or placed on an observation table.

The catheter was not employed in administering the liquid to guinea pigs. These were restrained by hand, the mouth opened, and the liquid introduced with a medicine dropper, whereupon the animal immediately swallowed the dose.

The details of the work were administered by a chemist, a pathologist and an ophthalmologist.

General Observations.—In running the tests with isopropanol careful comparisons were made with the effect of ethyl alcohol administered under identical conditions. With some subjects these substances were administered alternately, that is, one day the rabbit or chicken received a dose of isopropanol, and the next day ethyl alcohol. By this means, the individual susceptibility was determined and a better comparison of the reactions could be gained.

In every instance it was noted that at first the animal reacted more sharply to the isopropanol than it did to the ethyl alcohol. The first two or three doses of isopropanol might cause complete inertia and prostration, lasting sometimes for several hours, while with equivalent doses of ethyl alcohol, though there was usually a marked incoordination, coma never resulted.

It was interesting to note however, that after two or three administrations, the animals acquired a tolerance to isopropanol, and thereafter they reacted no more seriously than they did to ethyl alcohol. In one case, notably a chicken, the first dose of 20 c.c. of 50 per cent isopropanol produced a condition of collapse, lasting thirty-six hours. Recovery was complete, however, and the bird subsequently developed such a tolerance that she could ingest a similar quantity with no more effect than a well-defined incoordination of the legs. This subject received 280 c.c. of 50 per cent isopropanol between October 20 and November 30, 1921. During the observation she lost weight and had an unhealthy appearance, but on terminating the dosages, she recovered her health and apparently became normal with brilliant comb and wattles, and sleek plumage.

The effect of isopropanol on cats was extreme and almost immediate. They lost control of their hind legs and after floundering about for a short time, passed into a stupor from which they could not be aroused. After several hours they recovered and from that time, were apparently normal.

With dogs, the effect was delayed and these animals were much less susceptible to its effects than were cats. Incoordination was apparent, but they never exhibited the absolute stupor shown by the cats or the prostration that was rendered by the first few doses on rabbits.

The observations made on guinea pigs were not satisfactory. These creatures are small, and the individual susceptibility of the test animals varied to such an extent that it was difficult to control the dosage, and at the same time determine whether the reactions observed were due to an overdose of the product or to the sensitiveness of the animal.

Gross Pathology.—Most of the rabbits showed chronic passive congestion of the stomach, intestines, liver or kidneys, one rabbit showing the effects in one of these organs, another with a different organ. In some cases, inflammation of the stomach and intestines was also evident. These conditions occurred in both the isopropanol and ethyl alcohol subjects.

It will be noted from the detail summary below, that some of the subjects ingested a considerable bulk of isopropanol during the course of the investigation. It is not surprising, therefore, that chronic gastric pathogenesis was established. It would have been more remarkable had the introduction of a substance so foreign to the normal diet of the creature not set up some disturbance of the alimentary tract, or of the vital organs.

In some cases, blurring and "cupping" of the optical discs was noted, but this condition was found equally marked in case of the ethyl alcohol rabbits. The changes noted in the optical system are not of great moment and it should be emphasized that the effects of isopropanol in this respect are no more momentous than are those of ethyl alcohol. No evidence of blindness was apparent in any instance. It must be borne in mind, however, that the optical system of the rabbit differs in certain particulars from that of the higher animals. For this reason, careful special observations were made of the action of isopropanol on the optic nerve and the eye of the monkey and human being. The result of this last series of tests, to be later detailed, showed that not only was there no impairment of vision or other observable

effect, but in the case of the human subjects most of them reported that during the time of the trial, their ability to use their eyes was noticeably enhanced.

During the course of the work, careful observations were made of the condition of the urine with respect to the presence of acetone. On account of the quantity voided and the facilities attendant to its collection, only that of the dogs and human subjects was examined. It was found that the ingestion of isopropanol produced acetone in the system, the same being eliminated through the kidneys and found in the urine by chemical test. It appeared within twenty-four hours after ingestion, and was constantly present until the isopropanol was withdrawn, after which time no more was noted.

The appearance of acetone in the urine was at first the occasion of some concern, inasmuch as its presence is ordinarily an indication of a metabolic disturbance in the system, due to the breaking down of the fatty tissues. However, the reason for its presence in this case is obvious when the character of isopropanol is taken into consideration. It is well known to the physiologist that alcohols are oxidized in the body. And it is equally a matter of common knowledge to the chemist, that primary alcohols, such as ethyl alcohol, yield aldehydes on oxidation but that secondary alcohols do not; they are decomposed with the production of ketones, and if one glances at the structure of isopropanol (isopropyl alcohol) as noted herewith CH_3

$CHOH$, it is apparent at once that the products of its oxidation must be CH_3

acetone and water.

$$\begin{matrix} CH_3 \\ \\ CH_3 \end{matrix} CHOH + O = CH_3COCH_3 + H_2O.$$

The fact must be borne in mind that the presence of acetone in the urine of diabetics is not the cause for concern for the subject. The acetone is simply an indicator of a metabolic change that is taking place, and is a constant factor in the course of the disease. In the matter under discussion, the acetone is produced by an entirely different action going on in the system, and its presence ceases as soon as the ingestion is terminated.

Fate of Control.—During the entire course of the rabbit tests, a control animal was kept under observation, exposed to the same condition of temperature and environment, and fed with the same ration. The record began on September 20, 1921, at which time the animal weighed 2150 gm. and was in apparent good health. Its behavior throughout the period of observation was normal. On November 25, 1921, it was killed and autopsied, weighing on that date 2225 gm. The examination showed some coccidiosis, but otherwise the organs were normal.

It will be noted that this rabbit showed coccidiosis and that the same condition was observed in many of the rabbits used for these tests. For the benefit of the reader who may be unfamiliar with medical terms, it should be stated that coccidiosis is a condition of the liver usually peculiar

to rabbits, manifested by a pustular eruption. It occurs in rabbits that are kept under normal conditions just as frequently as it does in those being used for experimental purposes, and its presence is not a factor in judging the good or bad effects of the product under discussion.

TESTS ON MONKEY AND HUMAN BEINGS

Monkey.—The monkey selected was a white-faced capucin, not too small, but of such a size that restraint could be maintained without undue force, as the monkey is a very difficult animal to handle, and in its struggles may become more seriously injured by overexertion or mechanical contact, than by the test material. He weighed four pounds.

For this experiment the animal was kept under careful observation for two weeks until it became accustomed to the surroundings and the attendants, and was eating regularly. Restraint was maintained by holding the monkey in the hands protected by automobile gauntlets, two other attendants holding the hands and tail. The monkey soon became accustomed to swallowing the catheter and after a few days of struggling, submitted to the experiment with comparative ease in handling.

Doses of 5 c.c. of 50 per cent isopropanol were administered.

On January 19, 1922, the animal was given a dose in the amount above noted and soon developed mild symptoms of intoxication, followed by drowsiness and the indisposition to eat. This test was repeated November 23, with similar results. On the following day he was given 10 c.c. or double the quantity previously administered with the result that definite symptoms of intoxication became manifest, muscular incoordination, nausea, vomiting, extreme lassitude and indisposition to move occurred, lasting for about twenty-four hours. The animal was allowed to recover completely before further administrations.

Beginning January 27 and continuing until February 14, or thirteen days during the interval, doses of 5 c.c. were given. In every instance, the symptoms produced were mild and the animal had apparently established a considerable tolerance to the isopropanol.

The administrations were terminated February 14, and the monkey kept under clinical observation until June 29 when he was transferred to a large cage at the National Zoological Park. He was still alive on December 14. He has since died. In appearance he was greatly inferior to the other capucins, was thin and apparently in poor health, though he ate well.

The conclusions of the pathologist may be summarized as follows. The symptoms produced on the monkey are not unlike those produced by ethyl alcohol. Definite intoxication by isopropanol is seen. Gastroenteritis, with indisposition to eat, is met with in the case of ethyl alcohol as well as with isopropanol.

After each administration the animal was always more or less affected but to a much less degree of intensity in the later stages of the experiment than in the earlier. He would often lie in a corner of the cage for a while after receiving the dose, but his eyes were not always closed and consciousness of outside happenings was usually manifested.

The appetite was much affected, food being relished with less enthusiasm than before the period began.

As this experiment had for its special object, the study of the action of isopropanol on the optical system, the observations of the oculist are noted in detail.

Prior to the inauguration of the tests, it was observed that the right optic disc was somewhat more engorged than the left but the eyes were otherwise normal. After the first ingestion, the examination showed both optic discs congested but otherwise the eyes were normal. Subsequent examinations were virtually the same, always more or less congestive.

March 2, two weeks and a half after the test was terminated, the oculist reported that both eyes were apparently normal. The pathologist therefore asserts that isopropanol in the dosage given produced some congestive disturbances on the eyes, but no organic changes that would result in blindness.

Human Beings.—As the experiments thus far conducted had indicated that isopropanol was a substance of relatively low toxicity, and as it apparently had no effect on the optical system, it was decided expedient to note the reaction of human beings to its ingestion.

Grant and Johns of the Standard Oil Company in articles published in the *American Perfumer*, 1921, and the *American Journal of Pharmacy*, 1921, referred to Sinclair's tests of the local effects of isopropyl alcohol (isopropanol) on the skin of human beings, the conclusions of the authors being that it was without harmful action.

For the experiments to be described, there were selected healthy subjects, five male and two female. Their clinical history was readily obtained and checked during the course of the test, and being competent to make clinical observations and reports themselves, their personal experiences are of interest and are summarized.

These subjects reported for several days before being given the isopropanol, and their normal behavior, pulse rate, temperature, blood pressure, elimination and character of urine noted. Their eyes were also carefully examined and found perfect. At the end of the probationary period they were given doses of 20 to 30 c.c. isopropanol of 50 per cent strength, slightly sweetened and flavored to assist the mawkish taste characteristic of an unflavored mixture of water and isopropanol.

In general the immediate effect of the administration of isopropanol was a lowering of the blood pressure, both systolic and diastolic. Sometimes, however, a rise was noted, and the variation from normal was not consistent. After about half an hour the diastolic returned to normal, and often showed an increase over that observed before administration. This was more noticeable with the male than with the female subjects.

The pulse pressure was lowered. The pulse rate varied, sometimes rising and sometimes falling, the effect often being different on the same subject on different days.

There was little effect on the respiration. In some cases, it rose a few points and again it went down.

All of the subjects reported that almost immediately after taking the dose, a sensation of warmth pervaded the system. They became dizzy to a greater or lesser degree, but this soon disappeared. One man and one woman experienced a tingling sensation, especially in the arms and legs, that lasted for some time, and two other male subjects reported an anesthetic or numbing reaction.

Drowsiness occurred in three cases on the first day of the test, but a tolerance seemed to be established and thereafter no condition of this character was experienced.

Five subjects experienced headache of varying intensity, one woman in particular awaking from a sound sleep with a severe pain.

In all cases, the symptoms were the most severe and lasting on the first day of the test, but thereafter the effects wore off in from one to three hours. In one instance aside from the sensation of warmth, slight dizziness, numbness and heaviness of eyelids which soon disappeared, there was no reaction experienced.

Each morning before reporting at the laboratory, the subjects were examined by the oculist and for two weeks after the dosages were stopped, observations of the eyes were continued. No untoward effects occurred; in fact, as was noted previously with every subject there was an apparent greater clarity of vision established.

Urine examinations made prior to ingestion of isopropanol gave negative tests for acetone. During the course of the experiment, acetone appeared, just as it had been observed in the case of the dogs. As soon as the subjects ceased taking isopropanol the acetone disappeared. The explanation of the presence of this body in the urine has already been discussed.

CONCLUSIONS

We have thus noted in brief the observations of the effects of isopropanol on the animal economy when this substance is taken into the system at a strength which can be ingested by the subject without apparent local discomfort.

The animal economy is capable of absorbing isopropanol in reasonable amounts without the accompaniment of toxic results.

That the ingestion of the substance produces a form of intoxication especially in the early period of the test is apparent, the violence and duration of the same depending on the species.

It is clear, however, that in most instances, barring perhaps cats, a tolerance is quickly established, and thereafter the outward appearance of the intoxication differs in no respect from that produced by ethyl alcohol.

ACTION ON MICROORGANISMS

Action of Isopropanol on Bacteria Yeasts and Molds.—The question may naturally arise as to what evidence we possess that isopropanol will act as a preservative against the action of yeasts, molds and bacteria. To answer this query, a series of tests was instituted, which demonstrated that isopropanol would inhibit the development of mold and render dormant the spores to the same degree at least that is done by ethyl alcohol. As to its comparative action against yeasts and bacteria, the following chart shows that it has an inhibitory value of greater intensity than ethyl alcohol.

In the test against bacteria, increasing quantities were mixed with standard extract broth and inoculated with Bacillus typhosus. After incubation subcultures were made whereby the disinfectant effect was determined. In the fermentation tests only the inhibitory values were recorded.

TABLE I

RESULTS, SHOWING THE COMPARATIVE ACTION OF ISOPROPANOL AND ETHYL ALCOHOL AGAINST BACTERIA AND YEASTS

BACTERIA

Technic: Preparations in the following quantities were mixed with 10 c.c. of standard extract broth, inoculated with one standard (4 mm.) loop of a vigorous 24 hour broth culture of Bacillus typhosus "Rawlings"; cultured at 37.5° C. for 48 hours and observed for inhibition; subcultured on agar to determine disinfectant strength.

QUANTITY OF PREPARATION USED	ISOPROPANOL		ETHYL ALCOHOL	
	INHB. CULT.	SUB. CULT.	INHB. CULT.	SUB. CULT.
c.c.				
.1	+	+	+	+
.2	+	+	+	+
.3	+	+	+	+
.4	±	+	+	+
.5	±	+	±	+
.6	–	–	±	+
.7	–	–	–	+
.8	–	–	–	–
.9	–	–	–	–
1.0	–	–	–	–
1.1	–	–	–	–
1.2	–	–	–	–
1.3	–	–	–	–
1.4	–	–	–	–
1.5	–	–	–	–

YEASTS

Technic: Preparations in the following percentages of the substances mixed with standard fermentation liquor were planted with bakers' yeast and incubated 24 hours at 36° C.

PERCENTAGE MIXTURE	ISOPROPANOL	ETHYL ALCOHOL
7	+	+
8	+	+
9	+	+
10	+	+
11	+	+
12	+	+
13	+	+
14	–	+
15	–	+
16	–	+
17	–	–
18	–	–
19	–	–
20	–	–
21	–	–
22	–	–
23	–	–
24	–	–
25	–	–

Key: + indicates positive growth.
– indicates no growth.

DETAIL SUMMARY OF ACTION OF ISOPROPYL AND ETHYL ALCOHOLS ON ANIMALS

Rabbit-Control.—Observation started September 20, 1921, weight 2150 gm. Killed and autopsied November 25, 1921, weight 2225 gm. Behavior normal throughout period of observation. Gross pathology at autopsy: Some coccidiosis, otherwise, normal.

Rabbit No. 1.—Given 115 c.c. isopropyl alcohol in 5 c.c. doses. Observations begun Sept. 28, weight, 2075 gm., to Oct. 29, 1921, weight, 2000 gm. Symptoms: Slight incoordination at first with little drowsiness, otherwise no appreciable effects. Tolerance established later. Gross pathology: Some evidence of mild chronic gastrointestinal catarrh, with chronic passive congestion, otherwise apparently normal. Ophthalmologist reports both discs probably a little blurred.

Chicken No. 1-a.—Given 50 c.c ethyl alcohol. Usual effect of this drug noted; larger dose (20 c.c.) produced drunkenness of less profound nature than isopropyl doses. About 20 hours duration. Still living and in apparently good health.

Rabbit No. 2.—Given 220 c.c. isopropyl alcohol in 10 c.c. doses. Observations begun Sept. 28 (weight 1900); Oct. 10, 1921 (weight, 1630); to Nov. 25, 1921 (weight, 1930);

Oct. 12, 1921, last dose. Symptoms: Considerable incoordination at first, gradually decreasing as apparent tolerance established; ate very little at first; later no particular effect on appetite. Gross pathology: Old, but mild chronic gastritis; otherwise no particular changes evidenced. Ophthalmologist reports scar on left cornea and left disc decidedly blurred.

Chicken No. 2-a.—Given 280 c.c. isopropyl alcohol in 10, 15 and 20 c.c. doses. Observations begun Oct. 20, 1921. Still living and in good condition. Last dose 20 c.c., Nov. 30, 1921. Smaller doses produced well defined incoordination and symptoms of intoxication at first; 20 c.c. produced profound stupor lasting for 36 hours. Considerable tolerance established toward last. Lost weight and did not look healthy.

Rabbit No. 3.—Given 90 c.c. of isopropyl alcohol in 15 c.c. doses. At first showed rather rapid and pronounced incoordination and weakness of muscles, lasting 3 to 5 hours. Tolerance established to some extent towards last. Observations begun Sept. 29th, 1921 (weight 2050); died from hemorrhagic lobar pneumonia 10:30 A.M., October 6, 1921 (weight 1910).

Rabbit No. 5.—Given 170 c.c. isopropyl alcohol in 10 c.c. doses. Observations begun Oct. 4, 1921, (weight, 2050) to Oct. 29, 1921, (weight, 1920). Weight, October 14, 1921, 2060. Symptoms similar to No. 2. Ophthalmologist reports some cupping of disc, otherwise normal.

Rabbit No. 6.—Given 135 c.c. isopropyl and 135 c.c. ethyl alcohol in 15 c.c. doses alternating every other day. Observations begun Oct. 4, 1921, (weight 2270). Killed and autopsied Oct. 29, 1921 (weight 2000). Isopropyl produced quicker and more profound symptoms of intoxication; came on quicker and lasted longer. Gross pathology showed some chronic gastritis and chronic passive congestion of liver and kidneys. Ophthalmologist reported both cornea with parenchymatous changes and discs probably blurred.

Rabbit No. 7.—Given 85 c.c. of ethyl alcohol in 5 c.c. doses. Observations begun Oct. 4, 1921 (weight, 2200); killed and autopsied Oct. 29, 1921 (weight 2135). Symptoms: Slight incoordination, some drowsiness and indisposition to eat at first, not noticeable toward last. The ophthalmologist reported "Optic nerve yellowish; circulation good, cupping of disc marked." Gross pathology: Some chronic gastritis and chronic passive congestion of liver and stomach.

Rabbit No. 8.—Given 180 c.c. of ethyl alcohol in 10 c.c. doses. Observations begun October 4, 1921 (weight 2005). Killed and autopsied Oct. 29, 1921 (weight, 2050). Symptoms similar to above No. 7, except more marked. The ophthalmologist reported "Both cornea show marked interstitial changes." Gross pathology: Stomach shows considerable chronic passive congestion, chronic gastritis and some mottling.

Rabbit No. 10.—Given 210 c.c. isopropyl alcohol in 15 c.c. doses. Observations begun Oct. 7, 1921 (weight, 2200). Killed and autopsied Oct. 29, 1921 (weight, 1870). Symptoms: Pronounced incoordination; stupor well defined at first; fairly good tolerance established later. The ophthalmologist reports "No changes noted." Gross pathology: Stomach shows mild chronic gastritis with chronic passive congestion of liver; otherwise normal.

Rabbit No. 11.—Given 105 c.c. ethyl alcohol and 105 c.c. isopropyl alcohol in alternate doses of 15 c.c. each. Observations begun Oct. 11, 1921 (weight, 2250). Killed and autopsied Oct. 29, 1921 (weight, 2190). Symptoms: Quite similar to No. 6. Ophthalmologist reported: "Optic disc whiter than normal i.e., less capillary circulation, cupping marked." Gross pathology: Mild chronic passive congestion of stomach and liver.

Black Cat No. 28.—Given 125 c.c. of isopropyl alcohol (50 per cent) in 20 c.c. and 15 c.c. doses, beginning November 18, 1921 (weight, 2056 gm.). First dose 20 c.c., Nov. 18, 1921; 15 c.c., Nov. 22, 24, 25, 26, 28, 29, 30, 1921. Weight Nov. 30, 1921, 1925 grams. Animal very suceptible to the administration of the alcohol. Exhibited marked incoordination from 5 to 8 minutes after administration, beginning first in the posterior extremities and gradually involving the whole musculature. Animal became stuporous and 30 minutes later showed complete flaccid relaxation of muscles; respiration shallow and quite slow, ranging from 8 to 10 in the stuporous states. During administration animal showed no apparent

tendency to establish tolerance to the alcohol. Was nauseated and showed no disposition to eat. Eyes examined Nov. 29, 1921; no pathologic changes noted by the opthalmologist. Animal killed and autopsied Nov. 3, 1921. Thoracic and abdominal viscera showed considerable congestion, with subacute gastritis and enteritis, apparently from effects of the alcohol. Kidneys slightly swollen and congested. Liver showed some congestion with mild cloudy swelling. Lungs showed mild congestion, but no evidence of pneumonia or edema. Heart showed dilitation of right side. Brain shows mild congestion but otherwise apparently normal. Microscopic examination of kidneys, liver and brain confirm the gross examination. Cloudy swelling of kidneys, but no marked toxic effects. This animal, however, does not stand the administration of isopropyl alcohol as readily as dogs and rabbits.

White Dog No. 29.—Given 240 c.c. of isopropyl alcohol (50 per cent) in 30 c.c. doses. First dose given Nov. 18, 1921, and Nov. 21, 22, 25, 26, 28, 29 and 30, 1921. Weight of animal not determined. (Could not be satisfactorily weighed on scales in use.) Animal showed considerable incoordination, beginning from 5 to 10 minutes after administration, first noted in the posterior extremities. This was accompanied by a moderate amount of muscular weakness; considerable slobbering was observed. Some indisposition to eat was noted at times, but toward the end of the administration of the drug had no particular effect. Animal lost some weight, apparent from gross examination. Tolerance well established toward the latter doses. Eyes were examined Nov. 29, 1921, and no definite pathologic changes observed by the ophthalmologist. Dog showed some softening of the stool, but no evidence of passage of blood or other condition which might indicate gastro-enteritis. After discontinuance of the drug, animal made an uneventful recovery.

Gray Cat No. 30—Given 20 c.c. (50 per cent) isopropyl alcohol, Nov. 19, 1921; 15 c.c. Nov. 21; and 15 c.c. Nov. 22, 1921. Animal showed marked incoordination after first administration, with considerable muscular weakness beginning first in the higher extremities and finally involving the entire musculature. In addition to loss of muscular control, seemed to lose sense of relationship; would butt into the wall of the cage; finally developed stupor, with slowed respiration. The 15 c.c. doses did not produce quite so marked symptoms, but the usual symptoms were noted to a less extent. On Nov. 22, animal died from aspiration pneumonia due to break in catheter. Mucus membranes of abdominal viscera showed some congestion but no necrosis or ulceration; also some congestion of the kidney and liver of a mild nature. Death due to aspiration pneumonia with edema (accidental).

Yellow Dog, with Black Nose, No. 30.—Tests begun Jan. 19, 1922, with isopropyl alcohol (50 per cent). Given 15 c.c. Jan. 19, Jan. 20, Jan. 23, and 20 c.c. Jan. 24, 15 c.c. Jan. 25. Animal showed some incoordination after administration of the drug, with increased flow of saliva; some restlessness and irritation; exhibited no particular indisposition to eat, nor nausea. Stool became slightly softened. On Feb. 25, examination of eyes showed no evidence of pathologic change, except possibly slight congestion of the retinae. Animal did not appear to lose any weight. Preparation was discontinued after January 25, and animal kept under observation. From January 25 to February 24 no untoward pathologic condition noted; appeared to be a healthy dog except for mange which developed over head and right shoulder. On February 24, administration of 50 per cent ethyl was begun, 15 c.c. doses being given on Feb. 24, 25, 27, 28 and March 1. On the administration of the alcohol, animal exhibited symptoms of incoordination similar to that caused by isopropyl, but not so marked. Animal's eyes examined March 1 and found to be normal. Killed and autopsied March 1, 1922, with the following results: Exhibits mange over head, shoulder and right side. Thoracic and abdominal viscera normal in position. Liver enlarged, soft and friable; spleen normal. Stomach small; walls somewhat thickened. Definite gastritis, quite similar to alcoholic gastritis seen in human adults. Intestines show some congestion of a chronic passive nature. Pancreas red and congested—no other abnormalities. Kidneys slightly swollen; capsule strips with ease; cortex in fairly good condition. Heart shows dilitation of right ventricle; engorgement of right auricle. Lungs exhibit some chronic passive congestion. Brain exhibits a mild degree of congestion. No evidence of well defined pathology. Microscopic examination confirms the gross; shows some interstitial hepatitis, similar to beginning alcoholic cirrhosis of the liver, and slight parenchymatous

nephritis of the kidneys. Effects of alcohol on this animal are very similar to those seen in chronic ethyl alcohol poisoning in human adults.

Large Yellow Dog, with White Paws, No. 36.—Tests begun January 19, 1922, with isopropyl alcohol (50 per cent); given 25 c.c. on Jan. 19, 20, 22, 23, and 24. On February 25, began the administration of 50 per cent ethyl alcohol in 25 c.c. doses, being given Feb. 25, 26, 27, 28, and March 1, 2, 3, 4, 6, 7, and 8. Isopropyl alcohol administration begun again on March 9, and given on the succeeding days of March 10, 11, and 14. Animal killed by ether and autopsied April 29, 1922. Animal showed symptoms very similar to that of No. 30, with a tendency to establish some tolerance for the drug. Isopropyl alcohol appeared to be slightly more toxic than ethyl alcohol. No very serious pathologic manifestations were observed. Eyes were examined on February 25 and March 7, but showed no evidence of optic atrophy or retinal destruction, although some congestion was present. On autopsy the stomach showed chronic gastritis and chronic enteritis of long standing, quite similar to that seen in human adults who are alcohol addicts. Liver showed some congestion and an increase in fibrous tissue changes. Lungs and heart were grossly normal. Kidney congested; capsule thickened; stripped with slight difficulty; some interstitial changes of a chronic nature observed. Brain grossly normal except for a slight glazing of the pia mater. Eyes grossly normal except for some congestion of the choroid and retinal coats. Microscopic examination confirmed the gross findings, which indicate chronic changes produced by chronic alcoholism. The changes observed in this animal were not in any way unusual from those seen in chronic cases of ethyl alcohol intoxication.

ISOPROPYL ALCOHOL EXPERIMENTS ON HUMAN BEINGS

Subject No. 1. , Male

June 21, 1922

Before Administration:

Systolic blood pressure	125
Diastolic blood pressure	78
Pulse pressure	47
Pulse	92
Respiration	18

Dose at 12:52 P.M. of 20 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms:

1:00 P.M.

Systolic blood pressure	115
Diastolic blood pressure	74
Pulse pressure	41
Pulse	88
Respiration	18

1:12 P.M.

Systolic blood pressure	114
Diastolic blood pressure	72
Pulse pressure	42
Pulse	72
Respiration	20

Symptoms as Reported by Subject:

12:52 P.M. Burning sensation in throat.
12:53 P.M. Sensation of warmth in stomach.
1:15 P.M. Sensation of warmth in stomach still present.
1:20 P.M. Eructation of gas.

July 5, 1922.

Before Administration: 12:27 P.M.

	Systolic blood pressure	120
12:20 P.M.	Diastolic blood pressure	70
	Pulse pressure	50
12:27 P.M.	Pulse	76
	Respiration	18

Dose at 12:30 P.M. of 30 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms:

	12:47 P.M.	
	Systolic blood pressure	116
	Diastolic blood pressure	70
12:38 P.M.	Pulse pressure	46
	Pulse	68
12:47 P.M.	Respiration	16

	12:52 P.M.	
	Systolic blood pressure	108
	Diastolic blood pressure	74
12:52	Pulse pressure	34
	Pulse	66
	Respiration	16

Symptoms as Reported by Subject:

12:31 P.M. Burning sensation in throat.
12:33 P.M. Sensation of warmth in stomach.
12:34 P.M. Eructation of gas.
12:38 P.M. Eructation of gas.
12:40 P.M. Slight feeling of dizziness, lids of eyes feel heavy.
12:47 P.M. Eructation of gas.
12:53 P.M. Eructation of gas.
1:30 P.M. Eructation of gas.

July 6, 1922.

Before Administration:

12:18 P.M.	
Systolic blood pressure	116
Diastolic blood pressure	78
Pulse pressure	38
Pulse	80
Respiration	22

Dose at 12:20 P.M. of 30 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms:

	12:35 P.M.	
	Systolic blood pressure	108
	Diastolic blood pressure	76
12:33 P.M.	Pulse pressure	32
	Pulse	76
12:50 P.M.	Respiration	20

	12:50 P.M.	
	Systolic blood pressure	108
	Diastolic blood pressure	78
12:48 P.M.	Pulse pressure	30
	Pulse	80
12:50 P.M.	Respiration	22

Symptoms as Reported by Subject:

12:21 P.M. Burning sensation in throat.
12:22 P.M. Sensation of warmth in stomach.
12:23 P.M. Eructation of gas.
12:27 P.M. Eructation of gas.
12:30 P.M. Sensation of warmth about face.
12:37 P.M. Sensation of heaviness of eyelids.
12:38 P.M. Eructation of gas.
12:50 P.M. Increasing heaviness of eyes.
No other symptoms.

July 7, 1922.

Before Administration: 12:55 P.M.

Systolic blood pressure	115
Diastolic blood pressure	80
Pulse pressure	35
Pulse	74
Respiration	18

Dose at 12:56 P.M. of 30 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms: 1:11 P.M.

Systolic blood pressure	100
Diastolic blood pressure	76
Pulse pressure	24
Pulse	76
Respiration	18

1:26 P.M.

Systolic blood pressure	124
Diastolic blood pressure	76
Pulse pressure	48
Pulse	82
Respiration	20

1:37 P.M.

Systolic blood pressure	102
Diastolic blood pressure	74
Pulse pressure	28

Symptoms as Reported by Subject:

12:56 P.M. Burning sensation in throat.
12:57 P.M. Eructation of gas.
1:04 P.M. Light feeling in head.
1:06 P.M. Anesthetic feeling.
1:14 P.M. Feeling of heaviness of eyelids.
No other symptoms.

Urinalyses for Acetone:

June 22, 1922, P.M. Very good test.
June 23, 1922, A.M. Trace.
June 24, 1922, 7 A.M. Faint trace.
July 5, 1922, P.M. Good test.
July 6, 1922, A.M. Very good.
July 6, 1922, P.M. Strong, excellent test.
July 7, 1922, A.M. Fair.
July 7, 1922, P.M. Good.
July 8, 1922, A.M. Good.
July 8, 1922, P.M. Faint.
July 9, 1922, A.M. Faint.
July 9, 1922, P.M. Faint.
July 10, 1922, A.M. Faint
July 10, 1922, P.M. Trace.
July 11, 1922, A.M. Faint trace.

Eye Examinations:

June 21, 1922.

V O D = 20-15 c.c. = 20-15
V O S = 20-100 c.c. = 20-15
Fields normal for movement. Fundi normal.

June 26, 1922.

V O D = 20-15 with glass = 20-15
V O S = 20-70 with glass = 20-15
Field normal for form and motion. Fundi normal.
No evidence of any change since last examination.

July 8, 1922.

Eyes examined. Vision same. No change in either eye.

SUBJECT NO. 2. MALE

June 21, 1922.

Before Administration:

Systolic blood pressure	115
Diastolic blood pressure	55
Pulse pressure	60
Pulse	84
Respiration	18

Dose at 12:40 P.M. of 20 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms: 12:55 P.M.

Systolic blood pressure	106
Diastolic blood pressure	48
Pulse pressure	58
Pulse	68
Respiration	16

1:08 P.M.

Systolic blood pressure	104
Diastolic blood pressure	48
Pulse pressure	56
Pulse	72
Respiration	16

Symptoms as Reported by Subject:

12:40 P.M. Burning sensation in mouth and stomach.
12:48 P.M. Dull ache in stomach, slight lightheaded sensation and very slight dizziness, beginning of feeling of warmth to body.
12:52 P.M. Slight bitemporal headache.
1:00 P.M. Headache very slight.
1:05 P.M. Dizziness almost gone.
1:11 P.M. Headache disappeared.
1:15 P.M. Slight feeling of mental and physical dullness are only symptoms noticeable.

July 5, 1922.

Before Administration: 12:20 P.M.

	Systolic blood pressure	117
12:15 P.M.	Diastolic blood pressure	55
	Pulse pressure	62
12:20 P.M.	Respiration	20
	Pulse	70

Dose at 12:27 P.M. of 30 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms: 12:40 P.M.

	Systolic blood pressure	96
12:33 P.M.	Diastolic blood pressure	54
	Pulse pressure	42
	Pulse	70
12:40 P.M.	Respiration	14

12:56 P.M.

	Systolic blood pressure	98
12:48 P.M.	Diastolic blood pressure	56
	Pulse pressure	42
	Pulse	68
12:56 P.M.	Respiration	16

Symptoms as Reported by Subject:

12:27 P.M. Burning sensation from mouth to stomach.
12:33 P.M. Slight eructation of gas.
12:37 P.M. Feeling of slight dizziness.
12:42 P.M. Sensation of light headedness, very slight headache. Eyes feel heavy with desire to close them.
12:47 P.M. Began to feel sleepy.
12:57 P.M. More dizzy and much more sleepy, sleepiness progressing. Sleepy until about 3 P.M. No other symptoms after 3 P.M.

July 6, 1922.

Before Administration:

	Systolic blood pressure	98
	Diastolic blood pressure	58
12:24 P.M.	Pulse pressure	40
	Pulse	76
	Respiration	16

Dose at 12:24 P.M. of 30 c.c. 50 per cent isopropyl alcohol solution by mouth.

Objective Symptoms: 12:39 P.M.

	Systolic blood pressure	94
	Diastolic blood pressure	48
12:55 P.M.	Pulse pressure	44
	Pulse	78
	Respiration	20

12:55 P.M.

	Systolic blood pressure	96
	Diastolic blood pressure	52
12:55 P.M.	Pulse pressure	44
	Pulse	80
	Respiration	20

Symptoms as Reported by Subject:

12:26 P.M. Burning sensation in throat.
12:29 P.M. Feeling of warmth in stomach.
12:30 P.M. Feeling of haziness and dizziness.
12:35 P.M. Head feels very heavy. Sensation of warmth all over body.
12:40 P.M. Increasing dizziness, head feels large and full.
12:46 P.M. Cannot walk a straight line.
12:48 P.M. No headache at all, feel sleepy and head feels larger and heavier.
1:30 P.M. Very slight drowsiness remaining.
2:00 P.M. Cessation of all symptoms.

July 7, 1922.

Before Administration: 12:52 P.M.

	Systolic blood pressure	100
	Diastolic blood pressure	50
12:52 P.M.	Pulse pressure	50
	Pulse	74
	Respiration	18

Dose at 12:54 P.M. of 30 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms:

		1:09 P.M.
	Systolic blood pressure	100
	Diastolic blood pressure	44
1:09 P.M.	Pulse pressure	56
	Pulse	66
	Respiration	18

		1:24 P.M.
	Systolic blood pressure	96
	Diastolic blood pressure	42
1:24 P.M.	Pulse pressure	54
	Pulse	64
	Respiration	16

		1:33 P.M.
	Systolic blood pressure	94
1:33 P.M.	Diastolic blood pressure	48
	Pulse pressure	46

Symptoms as Reported by Subject:

12:55 P.M. Burning sensation in throat and warmth in stomach. Eructations of gas.

1:15 P.M. Do not feel any of the symptoms of dizziness, lightheadedness, as in previous experiments.

1:25 P.M. Very slight feeling of lightness in head and fullness in eyes.

1:45 P.M. Cessation of all symptoms. No further symptoms.

Urinalyses for Acetone:

June 22, 1922, 6 P.M. Very good test.
June 23, 1922, 7 A.M. Very good test.
June 24, 1922, 7 A.M. Very good test.
July 5, 1922, P.M. Trace.
July 6, 1922, A.M. Good test.
July 6, 1922, P.M. Good.
July 7, 1922, A.M. Very strong.
July 7, 1922, P.M. Very good.
July 8, 1922, A.M. Good
July 8, 1922, P.M. Faint.
July 9, 1922, A.M. Faint.
July 9, 1922, P.M. Faint.
July 10, 1922, A.M. Faint
July 10, 1922, P.M. None.
July 11, 1922, A.M. None.

Eye Examinations:

June 21, 1922.

V O D = 20–30 –1 = 20–30 with glass.
V O S = 20–30 –1 = 20–30 with glass.
Fields normal for movement. Fundi normal.

June 26, 1922.

V O D = 20–20 –3 = 20–20 with glass.
V O S = 20–20 –1 = 20–20 with glass.
Fields normal for movement and motion. Fundi normal.
No evidence of any change since last examination.

July 8, 1922.

Eyes examined. Vision better. No change in eye.

SUBJECT NO. 3. MALE

July 5, 1922.

Before Administration: 12:31 P.M.

	Systolic blood pressure	110
12:25 P.M.	Diastolic blood pressure	62
	Pulse pressure	48
	Pulse	62
12:31 P.M.	Respiration	20

Dose at 12:35 P.M. of 30 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms: 12:40 P.M.

	Systolic blood pressure	100
	Diastolic blood pressure	62
	Pulse pressure	38
	Pulse	66
	Respiration	16

1:05 P.M.

	Systolic blood pressure	102
12:57 P.M.	Diastolic blood pressure	64
	Pulse pressure	38
	Pulse	60
1:05 P.M.	Respiration	14

Symptoms as Reported by Subject:

12:35 P.M. Burning taste, burning sensation in nostrils.
12:36 P.M. Sense of warmth in esophagus and stomach.
12:39 P.M. Eructation of gas.
12:45 P.M. Slight sensation of lightness of head when standing.
12:52 P.M. Slight dizziness.
12:56 P.M. Slight drowsiness.
1:30 P.M. Drowsiness and dizziness disappeared.
3:15 P.M. Slight headache (frontal) especially about eyes, eructations of gas.
7:00 P.M. Headache quite severe.

July 6, 1922.

Before Administration: 12:15 P.M.

	Systolic blood pressure	108
12:13 P.M.	Diastolic blood pressure	62
	Pulse pressure	46
	Pulse	60
12:15 P.M.	Respiration	20

Dose at 12:18 P.M. of 30 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms: 12:35 P.M.

	Systolic blood pressure	92
12:29 P.M.	Diastolic blood pressure	60
	Pulse pressure	32
	Pulse	62
12:35 P.M.	Respiration	16

12:47 P.M.

	Systolic blood pressure	88
12:44 P.M.	Diastolic blood pressure	66
	Pulse pressure	22
12:47 P.M.	Pulse	60
	Respiration	20

1:00 P.M.

Systolic blood pressure	98
Diastolic blood pressure	68
Pulse pressure	30

Symptoms Reported by Subject:

12:19 P.M. Burning sensation in esophagus and stomach, sense of warmth in stomach.
12:32 P.M. Slight dizziness.
12:35 P.M. Heavy feeling about eyes.
12:44 P.M. Sensation of intoxication.
1:00 P.M. Slight headache.
2:10 P.M. Disappearance of all symptoms.

July 7, 1922.

Before Administration: 12:44 P.M.

Systolic blood pressure	105
Diastolic blood pressure	65
Pulse pressure	40
Pulse	66
Respiration	18

Dose at 12:49 P.M. of 30 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms: 1:04 P.M.

Systolic blood pressure	98
Diastolic blood pressure	70
Pulse pressure	28
Pulse	60
Respiration	16

1:19 P.M.

Systolic blood pressure	100
Diastolic blood pressure	66
Pulse pressure	34
Pulse	60
Respiration	16

Symptoms Reported by Subject:

12:50 P.M. Burning sensation in esophagus and stomach.
12:58 P.M. Sensation of light feeling in head, eructation of gas.
1:11 P.M. Slight dizziness and heaviness of eyelids.
1:30 P.M. Cessation of symptoms.

Urinalyses for Acetone:

July 5, 1922, P.M. Very good.
July 6, 1922, A.M. Good test.
July 6, 1922, P.M. Good.
July 7, 1922, A.M. Very good.
July 7, 1922, P.M. Good.
July 8, 1922, A.M. Good.
July 8, 1922, P.M. Marked trace.
July 9, 1922, A.M. Faint.
July 9, 1922, P.M. Faint.
July 10, 1922, A.M. Faint.
July 10, 1922, P.M. None.
July 11, 1922, A.M. Very faint.

Eye Examinations:

July 8, 1922.

V O D 20–20 with glass 20–30.
V O S 20–20 with glass 20–30.
No pathologic change noted in either eye.

SUBJECT NO. 4. MALE

April 22, 1922.

Before Administration:

Pulse	72
Respiration	26

Dose at 12:20 P.M. of 10 c.c. isopropyl alcohol by mouth.

Objective Symptoms: 12:37 P.M.

Pulse	80
Respiration	26

12:45 P.M.

Pulse	78
Respiration	24

Symptoms as Reported by Patient:

12:37 P.M. Slight sensation of flush. Eyes feel heavy.
Very slight dizziness on standing.
Sensation of warmth general.
Mild sensation of dryness of mouth.
1:30 P.M. Slight nausea in stomach.
2:00 P.M. Dull headache (slight).
2:40 P.M. Voided cloudy urine.
3:15 P.M. Headache gone, food taken.
5:25 P.M. Voided cloudy urine.
7:00 P.M. Voided slightly clouded urine.
10:00 P.M. Voided clear urine.

April 23, 1922.

1:00 A.M. Voided clear urine.
7:30 A.M. Voided clear urine.
9:30 A.M. Voided clear urine.
12:00 NOON. Voided clear urine.

July 5, 1922.

Before Administration: 12:28 P.M.

Systolic blood pressure	102
Diastolic blood pressure	70
Pulse pressure	32
Pulse	72
Respiration	22

Dose at 12:38 P.M. of 30 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms: 12:45 P.M.

Systolic blood pressure	88
Diastolic blood pressure	62
Pulse pressure	26
Pulse	80
Respiration	24

1:00 P.M.

Systolic blood pressure	90
Diastolic blood pressure	65
Pulse pressure	25
Pulse	80
Respiration	24

Symptoms as Reported by Subject:

12:40 P.M. Slight burning sensation in stomach.
12:42 P.M. Eructation of gas.

12:43 P.M. Feeling of dizziness.
12:44 P.M. Ringing sensation in ears.
12:45 P.M. Anesthetic feeling to skin.
12:46 P.M. Feeling of dizziness subsiding, ringing sensation in ears gone.
12:54 P.M. Feeling of drowsiness, gas in stomach.
12:57 P.M. Normal feeling returning.
1:20 P.M. Headache and increased drowsiness.
3:30 P.M. Severe headache and drowsiness.

Slept from 7:15 P.M. until 5:05 A.M.; awoke with headache; voided clear urine.

Summary of night: Was very dopy all evening, went to bed with a dull headache. Slept very well, awoke with the same headache, dry throat, no loss of appetite.

9:00 P.M. July 6, 1922. Headache gone.

July 6, 1922.

Before Administration: 12:10 P.M.

Systolic blood pressure	94
Diastolic blood pressure	66
Pulse pressure	28
Pulse	80
Respiration	24

Dose at 12:13 P.M. of 30 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms: 12:25 P.M.

Systolic blood pressure	96
Diastolic blood pressure	72
Pulse pressure	24
Pulse	80
Respiration	22

12:43 P.M.

Systolic blood pressure	95
Diastolic blood pressure	70
Pulse pressure	25
Pulse	72
Respiration	24

Symptoms as Reported by Subject:

12:15 P.M. Slight burning sensation in stomach.
12:16 P.M. Eructation of gas.
12:22 P.M. Slight sensation of dizziness.
12:28 P.M. Increased dizziness—numbness.
12:31 P.M. Warm sensation over body.
12:32 P.M. Dizziness lessening.
12:35 P.M. Slight nausea in stomach.
12:37 P.M. Feeling of drowsiness.
12:38 P.M. Feeling of drowsiness increasing.
12:47 P.M. Normal feeling returning.
1:30 P.M. All effect wearing off.
2:30 P.M. No effect. Feel normal.

July 7, 1922.

Before Administration: 12:54 P.M.

Systolic blood pressure	98
Diastolic blood pressure	70
Pulse pressure	28
Pulse	80
Respiration	20

Dose at 12:59 P.M. of 30 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms:

1:14 P.M.

Systolic blood pressure	100
Diastolic blood pressure	72
Pulse pressure	28
Pulse	82
Respiration	20

1:29 P.M.

Systolic blood pressure	96
Diastolic blood pressure	70
Pulse pressure	26
Pulse	80
Respiration	22

1:40 P.M.

Pulse	78
Respiration	18

Symptoms as Reported by Subject:

12:59 P.M. Tastes very hot, leaving burning sensation in throat.
1:02 P.M. Burning sensation in stomach.
1:03 P.M. Slight dizziness.
1:04 P.M. Increased dizziness with ringing sensation in ears.
1:05 P.M. Dizziness lessening, with perspiration.
1:06 P.M. Increased ringing sensation in ears.
1:07 P.M. Anesthetic feeling to body.
1:08 P.M. Increased feeling of numbness.
1:11 P.M. Eructation of gas.
1:17 P.M. Increased sensation of dizziness.
1:20 P.M. Slight inclination to giddiness.
1:25 P.M. Normal feeling returning.
1:30 P.M. Normal feeling after lunch at this time.
1:30 P.M. to midnight: Excessive odor of whiskey to breath.

Urinalysis for Acetone:

July 5, 1922, P.M.	Very good test.
July 6, 1922, A.M.	Good test.
July 6, 1922, P.M.	None submitted.
July 7, 1922, A.M.	Good test.
July 7, 1922, P.M.	Fair.
July 8, 1922, A.M.	Fair.
July 8, 1922, P.M.	Marked trace.
July 9, 1922, A.M.	Faint.
July 9, 1922, P.M.	Faint.
July 10, 1922	None submitted.

Eye Examinations:

April 22, 1922.

Eyes examined and found normal. Attention called to grave possibilities in experimenting with humans with alcohols—patient did not seem to appreciate possibilities according to oculist.

July 6, 1922.

V O D 20–30 with glass 20–30.
V O S 20–25 with glass 20–30.
Fields normal for movement. Fundi normal.

July 8, 1922.

Eyes examined. No changes of pathologic nature noted.

SUBJECT NO. 5. MALE

June 22, 1922.

Before Administration:

Systolic blood pressure	108
Diastolic blood pressure	80
Pulse pressure	28
Pulse	68
Respiration	24

Dose at 12:37 P.M. of 20 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms: 12:40 P.M.

Systolic blood pressure	106
Diastolic blood pressure	80
Pulse pressure	26
Pulse	76
Respiration	28

1:04 P.M.

Systolic blood pressure	106
Diastolic blood pressure	80
Pulse pressure	26
Pulse	72
Respiration	16

Symptoms as Reported by Subject:

12:39 P.M. Sensation of warmth in stomach; sensation of dizziness and slight loss of tactile sensation in fingers.

12:50 P.M. Warmth in stomach still persists. Still somewhat dizzy. Loss of sensation in fingers still present.

1:05 P.M. Slight headache.

1:15 P.M. Headache somewhat increased, but sensation of numbness leaving fingers. Feeling somewhat "dopy."

1:30 P.M. Headache decreasing and feeling practically normal.

Urinalyses for Acetone:

June 22, 1922, 7:30 P.M. Very good test.
June 23, 1922, 9:20 A.M. Very good test.
June 23, 1922, 8:00 P.M. Trace.
June 24, 1922, 9:00 A.M. None.

Eye Examinations:

June 22, 1922.

Fields normal for movement. Fundi normal.

July 8, 1922.

All examinations normal.

SUBJECT NO. 6. FEMALE

July 14, 1922.

Before Administration: 1:38 P.M.

Systolic blood pressure	132
Diastolic blood pressure	80
Pulse pressure	52
Pulse	80
Respiration	18

Dose at 1:50 of 30 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms: 2:18 P.M.

Systolic blood pressure	124
Diastolic blood pressure	78
Pulse pressure	46
Pulse	76
Respiration	18

2:23 P.M.

Systolic blood pressure	108
Diastolic blood pressure	72
Pulse pressure	36
Pulse	80
Respiration	20

Symptoms as Reported by Subject:

1:40 P.M. Disagreeable taste, afterwards resembling whiskey taste.
2:15 P.M. Sensation of warmth, slight tingling sensation in hands and feet which spreads over body and becomes slightly accelerated.
2:15 P.M. Eructation of gas with smoky taste, disappearance of sensation of wry-neck.
3:15 P.M. Sensation of pressure on top of head, feeling of relaxation with cold, clammy perspiration over body.
4:00 P.M. Headache, not severe, also slight nausea.
5:30 P.M. Sensation of hunger and thirst, dinner.
7:00 P.M. Normal feeling with exception of sensation of slight pressure on top of head, metallic taste in mouth all afternoon, increase of saliva, kidneys very active, amount of urine increased.

Urinalysis for Acetone:

July 14, 1922, A.M. None.
July 14, 1922, P.M. Good test.
July 15, 1922, A.M. Very good.
July 15, 1922, P.M. Fair.
July 16, 1922, A.M. None.
July 16, 1922, P.M. Very faint.
July 17, 1922, A.M. None.

SUBJECT NO. 7. FEMALE

July 14, 1922.

Before Administration: 1:48 P.M.

Systolic blood pressure	120
Diastolic blood pressure	84
Pulse pressure	36
Pulse	72
Respiration	24

Dose at 1:55 P.M. of 30 c.c. 50 per cent solution isopropyl alcohol by mouth.

Objective Symptoms: 2:12 P.M.

Systolic blood pressure	118
Diastolic blood pressure	76
Pulse pressure	42
Pulse	80
Respiration	24

2:27 P.M.

Systolic blood pressure	112
Diastolic blood pressure	74
Pulse pressure	38
Pulse	76
Respiration	24

Symptoms as Reported by Subject:

Dose at 1:55 P.M. No symptoms from medicine for ten minutes except slight stinging sensations to mouth. After ten minutes hands became cold and clammy and perspiration broke out over chest and head, particularly upper lip. Thirty minutes after a sense of lightness (rather slight) was experienced in the head and a rather carefree feeling, also a slight

tingling sensation in legs and arms which remained for about two hours. No further symptoms until 4:30 A.M., July 15, 1922, when she awoke with a very severe headache which could only be relieved with 10 grains of aspirin. No other symptoms.

Urinalyses for Acetone:

July 14, 1922,	A.M.	None.
July 14, 1922,	P.M.	Good test.
July 15, 1922,	A.M.	Good.
July 15, 1922,	P.M.	Not collected.
July 16, 1922,	A.M.	Not collected.
July 16, 1922,	P.M.	Not collected.
July 17, 1922,	A.M.	None.

STUDIES ON NEPHRITIS*

I. PHYSIOLOGIC AND ANATOMIC CHANGES FOLLOWING TEMPORARY ISCHEMIA OF THE KIDNEYS

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THIS work was undertaken as preliminary to the study of gastric secretory changes which occur in nephritis. As we desired to produce a nephritis without using toxins or chemicals, which per se might alter gastric secretion, we studied the effects of temporary occlusion of the renal blood vessels on the kidney, hoping thereby to produce a condition simulating nephritis.

Rowntree, Fitz and Geraghty[8] reviewed the literature up to 1913 and concluded that three facts had been established; namely, that following the complete or partial obstruction of the venous return from the kidney there results (a) albuminuria, (b) hematuria, if the lumen of the vein be greatly narrowed, and (c) the appearance of epithelial cells, singly, in groups, or as casts in the urine.

They found, on occluding the vein sufficiently to cause a congestion of considerable degree, that albuminuria occurred almost constantly, that casts and red cells were usually present, and that the phthalein and sodium chloride elimination was decreased, as was sometimes the amount of urine. They also found that sometimes more urine (low solids) was excreted from the congested kidney than from the normal kidney. In some cases, on histologic examination they found in the chronically congested kidney, small abscesses, and in one case, an increase in connective tissue; but on the whole they concluded that "chronic passive congestion of varying intensity is produced without an accompanying chronic nephritis." Guthrie[4] found that complete ischemia of the cat's kidney for ten minutes was much less harmful than perfusion of the kidney with normal saline or Ringer's solution. In one instance he observed almost complete degeneration of a kidney that had been perfused for about nine minutes. Eisendrath and Strauss[3] observed that temporary

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compression of the renal vessels of rabbits for thirty minutes or less caused very slight changes, but if continued for forty-five minutes or more, definite parenchymatous degeneration and interstitial infiltration resulted. Many observers—Litten,[5] Thorel,[10] Foa,[2] MacNider,[6] Bradford[1]—have studied and described the anatomic picture resulting from permanently ligating and clamping for long periods (one and one-half to twenty-four hours), all the kidney vessels or various branches of them. More recently Marshall and Crane[7] have reported that anemia of the kidney of short duration does not cause a prolonged anuria, and that anemia of one to three minutes has no effect on excretion of urine except for the appearance of protein in the urine. They found, however, that an anemia of twenty to twenty-five minutes caused decrease in the elimination of urea, phosphate, sulphate, creatinine and ammonia. Stoll and Carlson[9] performed a great number of experiments and found that anemia of the kidney for periods of from one to twenty minutes, caused anuria for varying periods following the release of the clamped vessels, and that the urine when it did appear, was distinctly dilute in character. They further observed a prolonged spasm of the renal vessels on releasing the renal artery after occlusion.

No observations have been made on the blood urea following ischemia of the kidneys, and the urine changes have not been followed for a long period of time following temporary occlusion (thirty to forty-five minutes).

METHODS

Female dogs were operated on (perineorrhaphy) in such a manner as to expose the urethral orifice. Such animals could be easily and aseptically catheterized. The dogs were put on a standard maintenance diet consisting of meat, bread and milk. (Control observations were made for from five to ten days prior to the operation at which the renal vessels were occluded.)

Blood urea was determined by Marshall's urease method. The specific gravity, acidity, chlorides, albumin, urea, and total nitrogen of the urine were determined. The elimination of phenolsulphonephthalein by the kidneys was studied, 250 c.c. of water being given by stomach tube prior to injecting the dye.

The blood vessels were occluded with a "bull-dog" clamp. The vessels between the clamp and kidney were palpated for pulsation after clamping and before removal of the clamp, in order to make certain that the clamp was and had been functioning. Occlusion was maintained for periods varying from one-half an hour to one hour, the abdomen being temporarily closed to prevent exposure of the intestines.

RESULTS

We have made observations on twenty dogs following occlusion of the vessels of the kidney for varying periods. In eight dogs, the blood urea was determined, the urine analyzed, and the phenolsulphonephthalein elimination followed, frequently. In twelve dogs the vessels of both kidneys were clamped for forty-five minutes, but only the objective symptoms, dye elimination, and pathologic anatomy were observed.

We will give very brief protocols of the eight dogs that we studied in more detail. The chlorides are expressed in grams per 100 c.c.; the albumin, in grams per liter (Esbach); the phenolsulphonephthalein elimination, in per cent eliminated in two hours; and the blood urea, in grams per 100 c.c.

Protocol, Dog. 2.—Vessels of both kidneys occluded for thirty minutes.

Nov. 21 to Dec. 8. Preliminary control period on a maintenance diet. Quantity of urine, 100 to 190 c.c.; sp. gr., 1040 to 1080; chlorides, 1.2 to 3.3; no albumin; no sugar; phenolsulphonephthalein elimination, 90 to 95; blood urea, 0.028 to 0.030.

Dec. 8. Occluded blood vessels of both kidneys for one-half an hour.

Dec. 9. Eighty-two c.c. urine by catheter; sp. gr., 1050; chlorides, 1.0; albumin, 0.4; no sugar; phenolsulphonephthalein elimination, 87; blood urea, 0.077; anorexia, and some vomiting.

Dec. 12. Urine, 97 c.c.; sp. gr., 1030; chlorides, 0.85; albumin, 0.4; no sugar; phenolsulphonephthalein elimination, 8.0.

Fig. 1.—Microphotograph from the right kidney of Dog 2, showing two dilated glomerular spaces filled with hyaline material and red blood corpuscles with absence of the glomerular tuft.

Dec. 15. Urine, 60 c.c.; albumin, 2.6; blood urea, 0.067. Dog is losing weight. Does not eat much and vomits occasionally.

Dec. 15 to Jan. 3. Average amount of urine, 60 c.c.

Jan. 3. Thirteen c.c. of urine by catheter; sp. gr., 1045; chlorides, 0.67; albumin, 2.0; phenolsulphonephthalein elimination, 60; blood urea, 0.130; very depressed and weak; coma, but no convulsions.

Jan. 4. Death. Autopsy. No gross pathology present, except that observed in the kidneys. Kidney vessels normal. Left kidney was less than half the normal size. Right kidney was normal in size and there were no gross changes on section. Histology: Left kidney shows areas of hyaline degeneration, congestion of and old hemorrhages about the tubules (clumps of hemotoidin); multiple small abscesses, chiefly in the medulla. Many blood vessels contain thrombi, some of which are being organized. Right kidney shows cellular detritus and casts present in a few of the tubules. Tubular epithelium in places shows degeneration and desquamation. A few of the glomeruli show degenerative changes, but they are not as marked as those in the tubules. There is some increase in medullary connective tissue.

Protocol, Dog 3.—Vessels of both kidneys occluded for forty-five minutes, followed six months later by removal of one kidney and trauma of the other.

Dec. 24 to 27. Preliminary control period on a maintenance diet. Quantity of urine, 150 to 175 c.c.; sp. gr., 1040; chlorides, 1.35 to 1.66; no albumin; no sugar; phenolsulphonephthalein elimination, 90 to 95; blood urea, 0.040 to 0.043. Weight 11.8 kg.

Dec. 27. Occluded vessels of both kidneys forty-five min.

Dec. 28. No spontaneous urine. Forty-five c.c. urine by catheter; sp. gr., 1050; chlorides, 0.83; albumin, 1.6; no sugar; phenolsulphonephthalein elimination, 40; blood urea, 0.043; anorexia, but no vomiting.

Dec. 31. Quantity, 275 c.c.; sp. gr., 1030; chlorides, 0.99; albumin, 0.5; phenolsulphonephthalein elimination, 80; blood urea, 0.030; appetite normal.

Dec. 31 to March 12. Observed daily. Normal.

March 12. Quantity, 300 c.c.; sp. gr., 1035; chlorides, 0.65; albumin, 0.5; phenolsulphonephthalein elimination, 70.

May 20. Quantity, 425 c.c.; chlorides, 0.45; albumin, negative; phenolsulphonephthalein elimination, 68; blood urea, 0.04. Animal in splendid condition.

June 25. Same as above, except for phenolsulphonephthalein elimination, which is now 64.

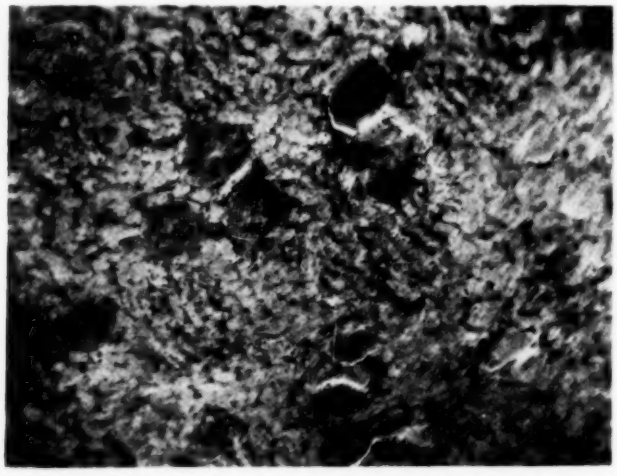

Fig. 2.—Microphotograph from the left contracted kidney of Dog 2, showing hemorrhage into the glomerular tuft and about the tubules and hyaline degeneration of the tubular epithelium. Other portions of the same section show connective tissue and lymphocytic infiltration about the glomeruli and hyaline material in the tubules.

July 17. Quantity, 325 c.c.; sp. gr., 1040; chlorides, 0.88; albumin, negative; phenolsulphonephthalein elimination, 64; blood urea, 0.035; physical condition excellent, weight, 16.2 kg.

July 22. Operation. Left kidney, which was less than one-half the normal size, was removed. Kidney vessels normal. The right kidney was bound to the liver and intestine by adhesions, which were severed.

July 23. Thirty-five c.c. of urine by catheter; sp. gr., 1055; chlorides, 0.76; albumin, 0.5; phenolsulphonephthalein elimination, 42; blood urea, 0.030.

July 24. Urine, 445 c.c.; sp. gr., 1040; chlorides, 0.71; albumin, 0.5; phenolsulphonephthalein elimination, 57; blood urea, 0.076. Dog does not eat and has an abscess of the mammary gland.

July 26. Urine, 325 c.c.; sp. gr., 1030; chlorides, 0.21; albumin, 1.0; phenolsulphonephthalein elimination, 34; blood urea, 0.141; dog vomits and does not eat.

July 28. Death. Autopsy. Peritonitis secondary to abscess of mammary gland, which infected the abdominal incision. The remaining kidney was of normal size, soft in consistency, congested, and the pelvis contained pus. Histology: The left kidney which was re-

moved at the operation shows an increase in connective tissue in areas chiefly in the medulla. There is an increase in the connective tissue about some of the glomeruli.

Protocol, Dog 4.—Vessels of both kidneys occluded for one hour.

Jan. 8 to 21. Preliminary control period on diet. Quantity of urine, 300 to 350; sp. gr., 1020 to 1035; chlorides, 0.60 to 1.07; blood urea, 0.032 to 0.050; no albumin; sugar, negative; phenolsulphonephthalein elimination, 70 to 75.

Jan. 21. Occluded blood vessels of both kidneys for one hour. Body weight, 8.5 kg.

Jan. 22. Anuria for twenty-four hours. Drinks water, but vomits.

Jan. 23. Some vomiting and anorexia. Quantity of urine, 190 c.c.; sp. gr., 1015; chlorides, 0.31; blood urea, 0.121; albumin, 0.5; no sugar; phenolsulphonephthalein elimination, 15; urine sediment; many kidney cells, few polymorphs, no casts or red blood cells, mucous shreds.

Jan. 25 to Feb. 3. Quantity of urine, 350 to 550 c.c.; other findings about the same as above except for phenolsulphonephthalein elimination, which is 33. Dog is losing weight and has a very poor appetite.

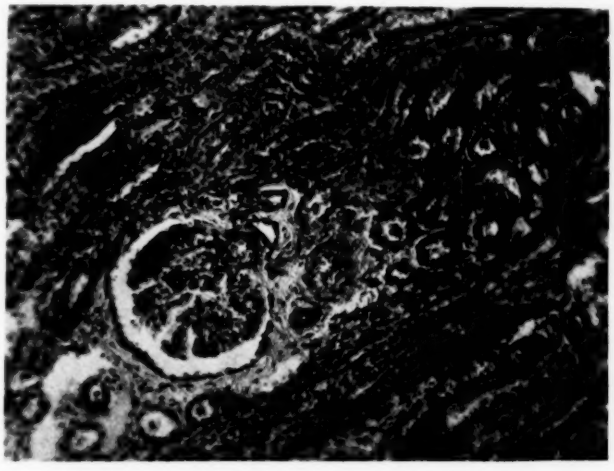

Fig. 3.—Microphotograph from the left kidney of Dog 3, showing an increase in the connective tissue about the glomerulus.

Feb. 9. Urine quantity, 300 c.c.; sp. gr., 1020; chlorides, 1.0; blood urea, 0.070; albumin, 0.05; phenolsulphonephthalein elimination, 66. Dog has gained weight and has a normal appetite.

Feb. 9 to April 9. Observations continued as above, weight, 10.8 kg.

April 9 to July 8. Quantity of urine, 425 to 650 c.c., sp. gr., 1020 to 1025; chlorides, 0.7 to 0.9; blood urea, 0.040; albumin, negative; phenolsulphonephthalein elimination, 67.

July 11. Dog accidentally killed. Both kidneys were white and contracted but only slightly less than normal in size. The cortex was pitted with areas of pale dense tough tissue. No tissue was saved for histologic examination. Renal arteries and veins normal.

Protocol, Dog 5.—Vessels of both kidneys occluded for one hour.

Feb. 8 to Feb. 13. Preliminary control period on diet. Quantity of urine, 430 to 450 c.c.; sp. gr., 1010 to 1015; chlorides, 1.0 to 1.25; blood urea, 0.034 to 0.044; no albumin; phenolsulphonephthalein elimination, 85 to 88; weight, 11.2 kg.

Feb. 14. Occluded blood vessels for one hour.

Feb. 15. Anuria and some vomiting.

Feb. 16. Quantity, 100 c.c.; sp. gr., 1008; chlorides, 0.23; blood urea, 0.128; albumin, 0.5; no sugar; phenolsulphonephthalein elimination, 34. Dog does not eat.

Feb. 18 to 20. Quantity, 250 to 375 c.c.; sp. gr., 1011 to 1012; chlorides, 0.34 to 0.65; blood urea, 0.055 to 0.056; albumin, 0.5; phenolsulphonephthalein elimination, 69. Smear of

urine sediment; renal cells, cellular casts, red blood cells and a few polymorphs. Dog does not eat.

Feb. 23. Quantity, 140 c.c.; sp. gr., 1018; chlorides, 0.35; blood urea, 0.093; albumin, 1.25. Smear of urine sediment; renal cells, but no blood. Anorexia and some vomiting.

Feb. 25. Same as above, except for albumin, which is 1.5. Weight of dog, 9.4 kg. Vomiting daily.

Feb. 27. Vomiting. Marked weakness and depression, followed by coma.

Feb. 28. Dog died. Autopsy. The left kidney is of normal size. On section it presents evidence of congestion and several small areas that appear to be necrotic. The right kidney is about half normal in size and has a pitted and speckled appearance. On section, many areas resembling small abscesses are seen. Approximately one-fourth of the kidney appears normal grossly. Renal arteries and veins normal. The pelvis of each kidney contains a small quantity of turbid fluid, but there is no evidence of inflammation. Urinary bladder normal. Ten c.c. of bloody fluid is in the pericardial space. The valve cusps are hyperemic. Five c.c. of clear fluid is present in each pleural cavity. The lungs markedly are everywhere edematous and congested. Ecchymotic hemorrhages are present in the mucous membrane of the stomach and colon. The brain is congested and more moist than normal.

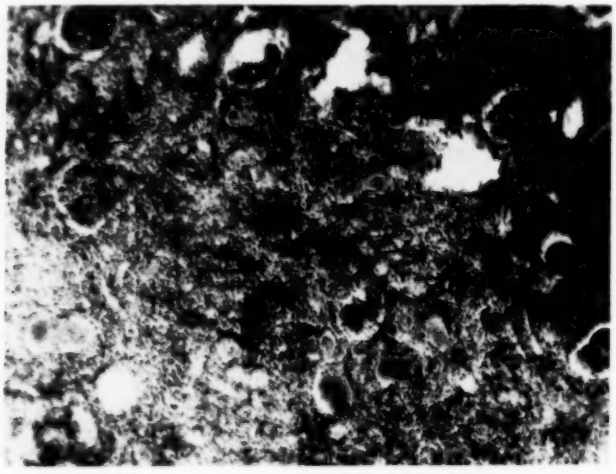

Fig. 4.—Microphotograph from the right kidney of Dog 5, showing marked degeneration of the tubular epithelium and hyaline material in the lumen of the tubules.

Histology of kidneys. Right kidney: Blood vessels of pyramids congested. Marked degenerative changes are present in some tubules. Hyaline degeneration is present in convoluted portion of other tubules. There are areas of tubular necrosis that are beginning to become calcified. Hyaline and cellular casts are present in some tubules. Left kidney: There are a few tubules that show degenerative changes, and a few areas of tubular necrosis showing evidence of calcification. Some of the glomeruli are hemorrhagic and white blood cells can be seen in the proximal tubules. The walls of the blood vessels are thickened in both kidneys and a few thrombi can be seen in the small arteries.

Protocol, Dog 6.—Blood vessels of both kidneys occluded one hour.

Feb. 25 to March 3. Preliminary control period on diet. Quantity of urine, 710 to 825 c.c.; sp. gr., 1020 to 1025; chlorides, 0.50 to 1.5; blood urea, 0.034 to 0.037; no albumin; no sugar; phenolsulphonephthalein elimination, 92 to 94.

March 3. Occluded vessels of both kidneys for one hour.

March 4. Does not eat, but vomits occasionally.

March 5. Quantity, 910 c.c.; sp. gr., 1007; chlorides, 0.25; blood urea, 0.136; albumin, 1.25; sugar, negative; phenolsulphonephthalein elimination, 47.

March 6. Quantity, 400 c.c.; sp. gr., 1011; chlorides, 0.25; blood urea, 0.103; albumin, 0.5. Dog does not eat and vomits occasionally. Urine sediment contains renal cells, but no casts.

March 8. Quantity, 300 c.c.; sp. gr., 1008; otherwise as above, except blood urea, which is 0.145, and chlorides, 0.10.

March 10. Does not eat, drinks much water and vomits occasionally. Quantity, 850 c.c.; sp. gr., 1008; albumin, 0.75; blood urea, 0.300; urine chlorides, 0.10.

March 12. Same as above. Blood urea, 0.255; phenolsulphonephthalein elimination, 38.

March 13. Since the dog was apparently in terminal coma, he was killed. Autopsy: The right kidney is approximately a fourth smaller than the left. The cortex is anemic and the pyramids congested. The left kidney appears normal grossly. No other gross pathology was evident. Histology. Right kidney: Many hyaline casts are in the tubules of the cortex. There are many more in the tubules of the medulla. A few glomeruli show slight hyaline degeneration. There are many small areas of small lymphocytic infiltration in the cortex, chiefly located near and about the glomeruli and blood vessels. The walls of the blood vessels are thickened and thrombi partially occlude some of the smaller arteries. Left kidney: Same changes are present as are described in right kidney, but not so extensively. Thin

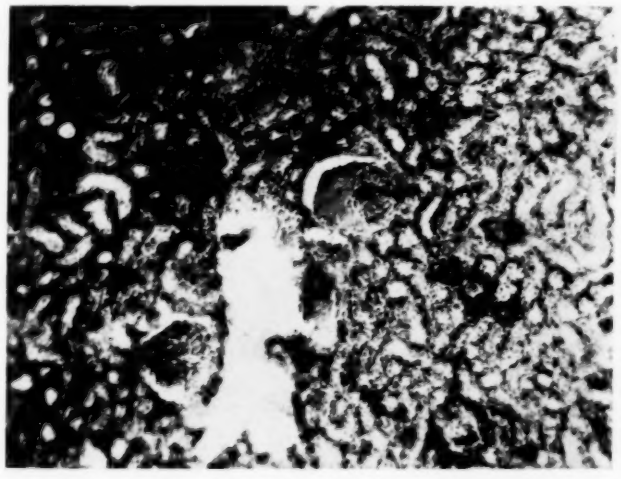

Fig. 5.—Microphotograph from the right kidney of Dog 6, showing hyaline material in the glomerular space and lymphocytic infiltration in and about the tubules.

paraffine section shows that the tubular epithelial cells are practically nongranular, and that some of them contain aggregates of material which stain similarly to the hyaline casts in the tubules.

Protocol, Dog 7.—Blood vessels of left kidney occluded one hour.

March 12 to 29. Preliminary control period on diet. Quantity of urine, 320 c.c. to 450 c.c.; sp. gr., 1025; chlorides, 0.55 to 0.48; blood urea, 0.068 to 0.072; no albumin; no sugar; phenolsulphonephthalein elimination, 75 to 80.

March 29. Occluded blood vessels of left kidney for one hour.

March 30. Fifteen hours after operation 150 c.c. urine excreted.

March 31. Quantity of urine, 150 c.c.; sp. gr., 1005; albumin, slightly positive; no sugar; chlorides, 0.30; blood urea, 0.085; phenolsulphonephthalein elimination, 80. Dog does not appear to be as sick as dogs in which both kidney vessels were occluded.

April 1. Quantity of urine 200 c.c.; sp. gr., 1020; albumin, 0.25; no sugar; chlorides, 0.32; phenolsulphonephthalein elimination, 70.

April 2. Quantity of urine excreted, 350 c.c.; sp. gr., 1025; albumin, 0.25; no sugar; chlorides, 0.32; phenolsulphonephthalein elimination, 70.

April 3 to 8. Quantity of urine excreted, 410 to 425 c.c.

April 8. Quantity of urine excreted, 450 c.c.; sp. gr., 1025; albumin, slightly positive; no sugar; chlorides, 0.9; blood urea, 0.035; phenolsulphonephthalein elimination, 73.

April 8 to 28. Quantity of urine excreted, 425 to 450 c.c.; no albumin.

Oct. 1. Killed. Left kidney one-third normal size. No histologic examination made.

Protocol, Dog 8.—Blood vessels of both kidneys occluded for one-half an hour.

April 24 to May 5. Preliminary control period on diet. Quantity of urine, 310 to 450 c.c.; sp. gr., 1025 to 1030; albumin, and sugar negative; chlorides, 0.81 to 0.92; blood urea, 0.040 to 0.048; phenolsulphonephthalein elimination, 72 to 81. Weight, 9.8 kg.

May 5. Blood vessels of both kidneys occluded for one-half hour.

May 6. Quantity of urine, 195 c.c.; sp. gr., 1020; albumin, 0.25; no sugar; chlorides, 0.37; blood urea, 0.045; phenolsulphonephthalein elimination, 65. Dog is depressed, does not eat, and vomits occasionally.

May 7. Quantity of urine, 217 c.c.; sp. gr., 1018; albumin, 0.5; no sugar; chlorides, 0.81; blood urea, 0.048; phenolsulphonephthalein elimination, 77. Dog still depressed and vomits occasionally.

May 8 to 11. Quantity of urine, 210 to 250 c.c.

May 12. Quantity of urine, 250 c.c.; sp. gr., 1025; albumin, 0.25; no sugar; chlorides 1.0; blood urea, 0.045; phenolsulphonephthalein elimination, 73.

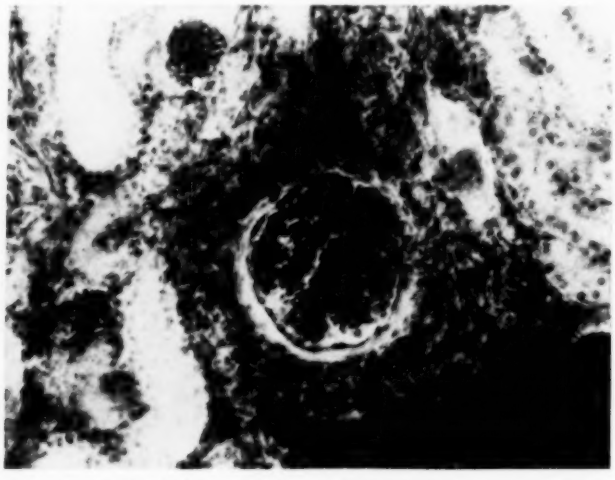

Fig. 6.—Microphotograph of the kidney of Dog 8, showing an increase in connective tissue and lymphocytic infiltration about the glomerulus.

May 14 to 19. Quantity of urine, 240 to 250 c.c.; sp. gr., 1022 to 1040; albumin and sugar, negative.

Aug. 20. Quantity of urine, 300 c.c.; sp. gr., 1040; albumin, 1.0; no sugar; blood urea, 0.018; chlorides, 0.87; phenolsulphonephthalein elimination, 59.

July 29. Dog was operated and Pawlow pouch made.

Aug. 21 to Sept. 5. Dog showed albumin in urine, 0.5 to 1.

Sept. 11. Quantity of urine, 290 c.c.; sp. gr., 1035; albumin, 0.5; no sugar; chlorides, 1.6; blood urea, 0.025; phenolsulphonephthalein elimination, 66.

Oct. 1. Killed. Autopsy. Changes not marked. Kidneys appear to be slightly smaller than normal and are scarred. Histologic examination reveals only small areas of connective tissue in the medullae and a few glomerular spaces that contain a hyaline material. There is an increase in connective tissue about many of the glomeruli.

Protocol, Dog 9.—Blood vessels of both kidneys occluded for one hour.

May 19 to May 26. Preliminary control period on the diet. Quantity of urine excreted, 250 to 275 c.c.; sp. gr., 1025; albumin and sugar, negative; chlorides, 0.48 to 1.2; blood urea, 0.042 to 0.057; phenolsulphonephthalein elimination, 86 to 90.

May 27. Blood vessels of both kidneys occluded one hour. Weight, 8.1 kg.

May 28. Eighteen hours after operation. Catheterized specimen, 22 c.c.; sp. gr., 1015; albumin, 1.5; no sugar; chlorides, 0.2; blood urea, 0.113; phenolsulphonephthalein elimination, 22. Dog is depressed, vomits, and does not eat.

May 29 to 31. Thirty c.c. obtained by catheter; sp. gr., 1015; albumin, 1.1; no sugar; chlorides, 0.4; blood urea, 0.033; phenolsulphonephthalein elimination, 50.

June 1 to 7. Dog has lost weight (7.6 kg.). Quantity of urine excreted, 210 to 320 c.c.; phenolsulphonephthalein elimination, 65.

June 19. Quantity of urine excreted, 300 c.c.; sp. gr., 1010; albumin and sugar, negative; chlorides, 0.51; blood urea, 0.035; phenolsulphonephthalein elimination, 38.

June 20 to July 23. About the same as above without notable change. Quantity of urine, 325 c.c.; sp. gr., 1010; albumin and sugar, negative; chlorides, 0.55; blood urea, 0.035; phenolsulphonephthalein elimination, 42.

July 28. Quantity of urine, 210 c.c.; sp. gr., 1018; albumin, slight trace; no sugar; chlorides, 0.5; blood urea, 0.03; phenolsulphonephthalein elimination, 54.

Aug. 20. Quantity of urine, 275 c.c.; sp. gr., 1021; albumin and sugar, negative; chlorides, 0.73; blood urea, 0.038; phenolsulphonephthalein elimination, 43.

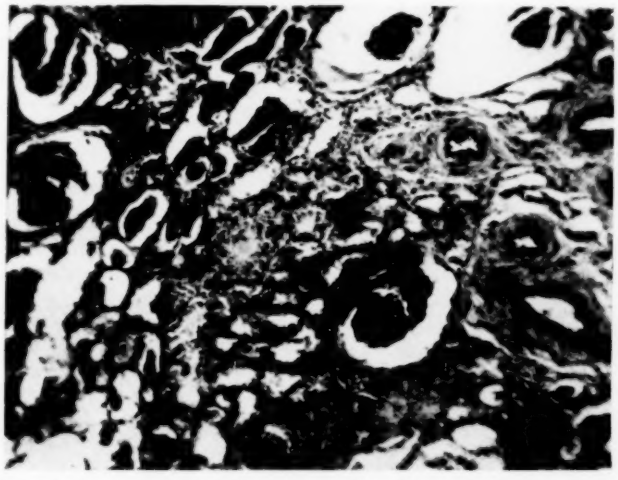

Fig. 7.—Microphotograph of the right kidney of Dog 9, showing hyaline material in the tubules and some of the glomerular spaces. In areas the tubules and hyaline material stain deeply blue, suggesting calcium deposition.

Aug. 26. Blood vessels of both kidneys clamped a second time for one-half an hour. On opening abdomen, dense adhesions had formed about kidneys and they were a great deal smaller in size.

Aug. 27. Eighteen hours after occlusion, anuria. Catheterized 12 c.c.; sp. gr., 1023; albumin, 1.0; no sugar; chlorides, 0.20; blood urea, 0.051; phenolsulphonephthalein elimination, 27. Dog depressed, does not eat, and vomits occasionally.

Sept. 3. Quantity of urine excreted, 255 c.c.; sp. gr., 1030; albumin, 1.0; no sugar; chlorides, 0.25; blood urea, 0.053; phenolsulphonephthalein elimination, 32. Dog does not eat very much food.

Sept. 11. Quantity of urine excreted, 285 c.c.; sp. gr., 1023; albumin and sugar, negative; chlorides, 0.56; blood urea, 0.046; phenolsulphonephthalein elimination, 41.

Oct. 1. Killed. Autopsy. Both kidneys scarred, white and contracted, the right kidney being more so than the left. Histology. Right kidney: There are extensive areas in the cortex in which there is great destruction of the parenchymatous tissue. Many of the glomeruli are replaced by a clear hyaline material and are crowded together so that ten or more glomeruli come into contact with one another. In these areas as well as in the tubules of the medulla there are many hyaline casts. In the cortex in the areas that show much degenera-

tion, there are small clumps of material that stain deeply blue, suggesting calcification. There is an increase of connective tissue about a few of the glomeruli and in the medulla. Left kidney: The same condition is present as described above in the right kidney, but not so extensively.

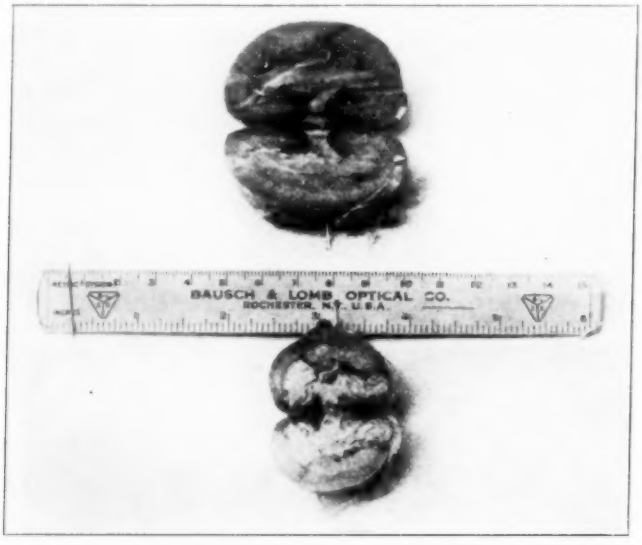

Fig. 8.—Kidneys taken from Dog 9 that had the circulation of both kidneys occluded for sixty minutes.

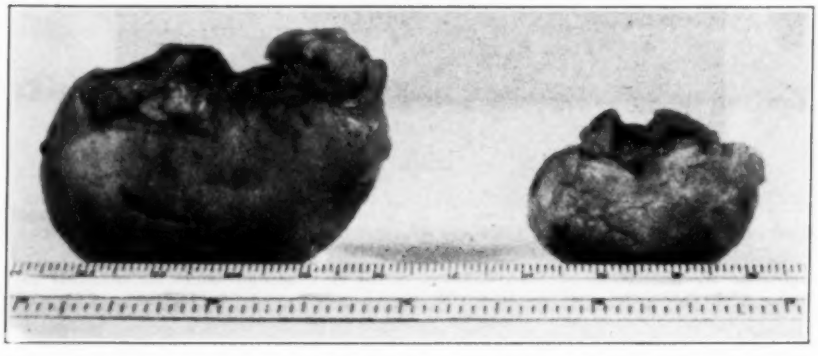

Fig. 9.—Kidneys taken from Dog 2 that had the circulation of both kidneys occluded for thirty minutes.

In the second group of twelve dogs, in which the kidney vessels were clamped for forty-five minutes, all survived the operation with the exception of two that died during the second week following the operation. Some of these dogs showed marked symptoms of anorexia and vomiting, lasting from four to five days; others, only mild symptoms lasting one or two days. In the first twenty-four hours it was almost always necessary to catheterize in order to obtain a sample of urine. Albumin was present in the urine from two weeks to a month following the operation. Many renal cells were present in the urine, but casts were few and were found with difficulty. Sugar

was examined for, but was never found. The normal elimination of phenolsulphonephthalein in this group varied from 70 to 90 per cent. The second day after the operation, elimination varied from 16 to 30 per cent; the seventh to fourteenth day, it varied from 50 to 70 per cent. No return to normal was observed. Anatomically one kidney was always apparently affected more than the other. In one case the left kidney weighed 6.5 gm., the other 2.2 gm. Also some dogs showed greater atrophic changes than others.

SUMMARY OF RESULTS

A dog may or may not survive clamping of the kidney vessels for periods of from thirty to sixty minutes. Whether or not survival occurs depends upon unknown factors governing the susceptibility of the animal to such a procedure. Physiologic and anatomic changes occur even after an ischemia of thirty minutes, one out of two dogs with such treatment, dying twenty-seven days after the operation. Eleven out of thirteen dogs survived the forty-five minute ischemia of the kidneys for indefinite periods. Two out of four dogs survived the sixty-minute ischemia for indefinite periods, the other two survived fourteen and sixteen days.

The chief objective symptoms following the ischemia of the kidneys were anorexia, vomiting and asthenia. The symptoms were more marked following an ischemia of sixty minutes than of a shorter period. One of the animals that survived manifested these symptoms at intervals for a month after the operation. The symptoms were most severe for the first three or four days, except in those animals that died within two weeks after the operation, in which the symptoms continued without abatement until death. Three animals died in coma.

The blood urea was increased following the operation in every case, except in Dog 8. In Dog 7, there was only a slight increase in the blood urea twelve hours after the clamping of the vessels of one kidney for our hour. In the dogs that did not survive the operation, the blood urea increased up to the time of death, being as high as 0.300 gm. in one. In those that survived, the blood urea returned to normal as the objective symptoms subsided.

No urine was voluntarily passed during the first twenty-four hours after the operation. However, at this time (eighteen to twenty-four hours) from 30 to 60 c.c. of urine could usually be obtained by catheter. Catheterization at twelve hours, in every case that it was done, either failed to demonstrate the presence of urine in the bladder, or resulted in obtaining amounts less than 5 c.c. Dog 7 must be excepted, but in this animal, the vessels of only one kidney were clamped.

The permanent effect of the ischemia on the quantity of urine was variable and no generalization can be made.

The urine chlorides were decreased in the majority of cases, no change occurring in Dog 7, and only a temporary decrease in Dog 8.

No noteworthy change was observed in the specific gravity of the urine.

Albumin, a few red cells and many kidney cells were present in the urine during the first week. The red cells usually were absent after twenty-four hours. Kidney cells persisted for from five to twelve days. Albumin

was present for from three weeks to four months. In one dog an operation after the disappearance of albumin from the urine caused it to reappear. Casts could be found only with difficulty.

Although we followed the total nitrogen and the urea of the urine, the results were so variable because of the vomiting, anorexia, etc., that they proved nothing. The results in general suggested what might be predicted, that during the period following the operation, in which the animal showed symptoms and a high blood urea, there was a decreased elimination of urea and total nitrogen.

During the time that the kidney vessels were occluded, the kidney would swell and become dark in color. On releasing the clamps, the normal color of the kidney would slowly return, appearing normal at least throughout the visible surface of the kidney.

Anatomic changes of the kidney occurred after a thirty-minute occlusion of the blood vessels of the kidney, but the changes were more extensive following a sixty-minute occlusion. Both kidneys were not usually injured to the same degree and different portions of the same kidney were not affected alike. In most sections, the inner portion of the cortex manifested more injury than the subcapsular portion. It was impossible for us to arrive at a generalization as to whether or not the tubular epithelium was affected more than the glomerular. The results show that anatomically, the occlusion of the blood vessels of the kidney results in a degenerative process that leads to what is commonly called a "small white kidney."

DISCUSSION

To us, one of the most striking findings in these results is the marked difference in the reaction of the kidneys of the same animal to the identical procedure. Since we are certain that the clamps did not slip, that no permanent injury of the renal artery or vein resulted from the clamping, and that it was not the same kidney in different dogs that showed the most atrophy, the only way we can account for this difference is, to assume that the collateral circulation of the least injured kidney was superior to that of the other kidney.

In a general way the effect of ischemia on the anatomy of the kidney as observed by us, confirms the observations of Guthrie, and of Eisendrath and Strauss, and is to be expected in view of the effect of prolonged ischemia on parenchymatous tissues in general. We were surprised to find that a sufficient amount of kidney tissue frequently survived a sixty-minute ischemia to maintain the animal in a normal condition for five months after the acute symptoms disappeared. Our observations of the development of what apparently appears to be a secondarily contracted kidney, directs attention to the fact that such a process occurred in our experiments independent of systemic infection. Thus the changes are to be accounted for purely by the ischemia, which may be further prolonged by a "postanemic" spasm following removal of the clamps (Carlson and Stoll). Can these observations be related to the view of Volhard[11]; that the changes in acute nephritis are due to an ischemia produced by a toxic agent that causes spasm of the vas afferens?

It is obvious from our results that a picture simulating acute parenchymatous nephritis can be produced in the dog by occluding the blood vessels of the kidney for thirty minutes or more. Hence, it is possible for us to study the effect of such a nephritis on gastric secretion.

Our results further show that in operations on the kidney neither clamps nor forced traction should be applied to the kidney pedicle for prolonged periods of time—certainly not longer than thirty minutes. Our observations may account for some of the small white kidneys found at autopsy, or by a second operation, in those cases in which the kidney had been previously operated upon.

SUMMARY

Ischemia of the kidney for periods of from thirty to sixty minutes in the dog causes degenerative changes that frequently result in the formation of a "small white kidney." Both kidneys are usually not affected to the same extent, the most probable explanation for the difference being a variability in the amount of collateral circulation. Dogs may or may not survive a thirty to sixty minute period of ischemia of both kidneys. The majority, however, survive an ischemia of forty-five minutes. The symptoms that result from such a procedure are vomiting, anorexia, asthenia and anuria. Albumin and cells (kidney cells, red and white blood cells) are present in the urine for varying periods of time. Albumin persists for from one to four months. The blood urea is always increased, and in the cases in which a severe reaction occurs, it may be as high as 0.300 gm. We believe that this method for the production of nephritis is most satisfactory for the study of the effect of nephritis on gastric secretion, or on other physiologic processes, in which it is necessary to avoid the use of toxins or chemicals, which per se might complicate the result.

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STUDIES ON NEPHRITIS*

II. GASTRIC SECRETION IN NEPHRITIS

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THE occurrence of gastrointestinal disturbances in the course of nephritis is well recognized by clinicians. The symptoms have been ascribed to an edema of the gastric mucosa, and also to the influence of the uremic condition on the central nervous system. Von Noorden[1] suggests, a greater part of the symptoms are due to the action of toxins on the gastrointestinal mucosa. In cases of anuria, numerous observers[1] have noted that substances usually excreted by the kidney are eliminated by the alimentary tract. Of these substances, the most irritating is ammonia, which is formed in the intestine by the decomposition of the urea that is eliminated. The feces in uremic diarrhea contain much ammonia.

Several writers have reported the results of gastric analysis in cases of acute and chronic nephritis with edema and in the acute relapses of interstitial nephritis. Biernacki[2] found that the secretion of HCl, rennin and pepsin to be diminished. Von Jaksch[3] noted a deficiency in HCl. Von Noorden[1] found an excess of HCl after meals in four out of nine patients with acute nephritis. Krakow[4] observed that in twenty-six cases of diffuse nephritis HCl was never absent and was diminished in eight cases. Zipkin[5] recorded similar results in twenty-three cases. One of Von Noorden's assistants (M. Dapper) studied gastric secretion in fifteen renal cases. In three, there was an absence of free HCl; in seven it was diminished; and in the others it was normal.

We have sought to determine the changes that occur in the secretion of gastric juice in cases of nephritis in man and in Pawlow pouch dogs on the production of an experimental nephritis without the use of toxic agents.

METHOD

In our experiments on animals Pawlow pouch dogs were used. The nephritis was produced by occluding the blood vessels of the kidney for various periods of time.

Van Slyke and Cullen's modification of Marshall's urease method was used for determining blood urea. The same method was used for determining the urea of the gastric juice, the free acidity of the gastric juice being neutralized completely and the combined acidity in part, so that the acidity was not more than 0.009 per cent. We always set up two tubes, one (a) with gastric juice plus enzyme, the other (b) with gastric juice without

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enzyme. We subtracted the latter result from the result obtained in "a" in order to arrive at a correct figure for urea. This was necessary because gastric juice contains ammonia.

EXPERIMENTAL OBSERVATIONS

The Effect of Experimental Nephritis on Gastric Secretion.—Two Pawlow pouch animals were studied. After a preliminary control period, during which the gastric secretory response to a standard meal and 1 mg. of histamine was determined, the blood vessels of the kidneys were clamped forty-five minutes; a procedure that causes nephritis.[9] Following the clamping of the kidney vessels, the blood and urine were studied simultaneously with the gastric response to a meal and to 1 mg. of histamine.

It is quite clear from the results shown in Table I that the type of acute nephritis produced by our procedure decreases, but does not abolish, the

TABLE I

THE EFFECT OF NEPHRITIS CAUSED BY OCCLUSION OF THE BLOOD VESSELS OF THE KIDNEY ON GASTRIC SECRETION

PAWLOW POUCH DOGS

DOG	METHOD OF EXCRETING GLANDS	BEFORE KIDNEY INJURY GASTRIC SECRETION			AFTER KIDNEY INJURY GASTRIC SECRETION			REMARKS
		AMT. C.C.	FREE ACID	TOTAL ACID	AMT. C.C.	FREE ACID	TOTAL ACID	
Dog 3	Meal	25	87	110	11	37	76	Dye elim. 34%.
	Histamine	16	80	90	15	46	87	Blood urea,
					11	21	37	0.141 gm.
Dog 9	Meal	12	51	75	8	33	65	Dye elim. 38%.
	Histamine	11	40	85	6	35	71	Blood urea,
								0.112 gm.
		SECOND CLAMPING						
	Meal	12	70	95	10	60	78	Dye elim. 32%.
	Histamine	18	40	65	11	30	57	Blood urea,
								0.053 gm.

Histamine secretion collected for two hours.

Meal secretion collected for two hours. Acidity expressed in clinical units.

Results recorded before kidney injury are averages of at least ten meal responses and two histamine responses.

After kidney clamping we give typical experiments as the dog would not eat at all times. The histamine responses are averages. Normal dye elimination in these dogs was from 85 to 90 per cent.

TABLE II

EFFECT OF INCREASED BLOOD UREA ON THE UREA CONTENT OF GASTRIC JUICE

PAWLOW POUCH DOGS

DOG	BEFORE KIDNEY INJURY		AFTER KIDNEY INJURY		REMARKS
	UREA IN BLOOD	UREA IN GASTRIC JUICE	UREA IN BLOOD	UREA IN GASTRIC JUICE	
Dog 9	0.057		0.113	0.060	
	0.054		0.114	0.132	
			0.035	0.012	After recovery
			0.038	0.014	
			0.050	0.026	Clamped kidneys
			0.052	0.024	again ½ hr.
			0.046	0.017	
Dog 3	0.024	0.010	0.030	0.015	
	0.027	0.011	0.080	0.026	
			0.141	0.039	Death

TABLE III

EFFECT OF INTRAVENOUS INJECTION OF UREA ON THE UREA CONTENT OF GASTRIC JUICE
PAWLOW POUCH DOGS

	UREA IN JUICE BEFORE INJECTION	UREA IN JUICE AFTER INJECTION	REMARKS
Dog 1	10 mg.	92 mg.*	Secretion stimulated by histamine
Dog 2	2 mg.	69 mg.	Secretion stimulated by histamine
Dog 3	10 mg.	20 mg.	Secretion stimulated by histamine
Dog 4	0 mg.	2 mg. 19 mg. 7 mg. 5 mg.	5 min. after 10 " " 15 " " 20 " " Secretion stimulated by histamine

Two grams of urea in 20 c.c. of normal salt solution were injected intravenously. The urea in the juice is expressed in milligrams per 100 c.c. of juice. Dog 4 had a pouch of the entire stomach, which made it possible for us to collect large quantities of secretion at five minute intervals. Repeated this experiment four times with similar results, the highest concentration appearing during the 10 to 20 minute period.

*Nephritis had been produced in this animal by clamping the kidney vessels two months previous to this experiment. Dogs 2, 3 and 4 were normal.

secretory response to a meal. Only typical results are shown in the table of the response when the animal ate the entire meal. As recovery occurred the response gradually returned to normal (Dog 9). No permanent damage of the gastric glands resulted.

Histamine was used to determine whether or not the gastric glands were fundamentally intact. This procedure could be and was used when the animal refused food. Both animals when they were sick, i.e., manifested anorexia, some vomiting, and a high blood urea, responded to histamine, but not normally, the amount of secretion being decreased more than the acidity. As recovery occurred the response returned to normal. This further shows that no permanent damage of the gastric glands resulted.

Urea in Gastric Secretion.—While ascertaining the effect of intravenously injected urea per se on gastric secretion, which is negative in the doses used, it was found that small amounts of urea (0 to 10 mg.) are present normally in the secretion of a Pawlow pouch. We then decided to ascertain if any quantitative relationship existed between the urea concentration of the blood and gastric secretion.

The results shown in Tables II and III show that the higher the concentration of urea in the blood, the higher the concentration in the gastric juice.

Although it would be very interesting to find whether or not a definite ratio exists, we have not as yet attempted to answer this question. Many more observations than we have made would be necessary to establish such a ratio. It is interesting to note (Table III) in this connection that the animal in which most urea was eliminated in the gastric secretion was Dog 1 with experimental nephritis. The result on Dog 4 in Table III suggests that there is a latent period of about five minutes before elimination by the gastric mucosa is initiated.

TABLE IV

GASTRIC SECRETION IN PATIENTS WITH NEPHRITIS
LACTOSE-TEA MEAL

PATIENT	GASTRIC SECRETION: FREE ACID	GASTRIC SECRETION: TOTAL ACID	REMARKS
Case 1. Mrs. L. G. Chronic interstitial nephritis Non-N-Salt free diet	trace	20	N.P.N. –53.2 mg. Urea N–25.8 mg. Creatinine –1.3 mg. Chloride 509 mg.
Case 2. Mrs. R., age 59 Chronic interstitial nephritis with hypertension	20	25	
Case 3. Mrs. D. Chronic nephritis	25	30	
Case 4. Chas. K. Nephritis with edema Chronic Age 18	45	65	N.P.N. –153.1 mg. Urea N –122 mg. Uric acid –6.2 mg. Creatinine 5.4 mg. Patient died, uremia
Case 5. Age 13 Acute nephritis with edema and uremic vomiting	35 25 18	75 30 28	Blood pressure 204 systolic Patient died Analysis of vomitus
Case 6. R. B. Age 14 Chronic nephritis with edema	16	24	N.P.N. –57 mg. Urea N –32 mg. Creatinine –2 mg. Chlorides –717 mg. Urine albumin –0.6%

Patients from the service of Drs. A. Edwards and Solomon Strouse, Michael Reese Hospital, Chicago.

CLINICAL OBSERVATIONS

The Effect of Nephritis on Gastric Secretion.—Eighteen cases of nephritis have been studied.

In six cases (Table IV) the response to a lactose-tea meal was determined. Free acid was found in every case, even in Case 5 with uremic vomiting.

The continuous gastric secretion (not gastric contents) was examined in twelve cases. Free acid was present in three of the cases (see Tables V and VI), it being as high as 80 clinical units in a patient that died several days later because of the severity of his nephritis.

The gastric response to histamine was observed in three cases (Table VI). An increase in the quantity of secretion occurred in every test. An increase in acidity occurred in every test except one (F.S.). Two days later, however, in the same patient under practically the same conditions histamine caused an increase in acidity.

Urea in the Gastric Secretion of Patients with Nephritis.—It should be pointed out that in collecting gastric secretion for these analyses the stomach was emptied and the contents discarded; the patient was then instructed not to swallow his saliva; the secretion was then collected for half an hour, and kept under toluol for about four hours before it was possible to examine it. Because of the possibility of the contamination of the gastric secretion with salivary urea, in spite of our attempts to prevent it, the results cannot be considered as exact as the results on Pawlow pouch dogs.

Our findings in patients (Tables V and VI) approximately parallel our findings on dogs (Table II), the higher the blood urea concentration, the

TABLE V

CONTINUOUS GASTRIC SECRETION IN NEPHRITIS AND THE AMMONIA AND UREA CONCENTRATION OF THE GASTRIC JUICE

PATIENTS

PATIENTS	GASTRIC JUICE		NH_3 MG.	UREA MG.	URINE AND BLOOD
	FREE	TOTAL	PER 100 C.C.	PER 100 C.C.	
D. Mc L. Age 32 Chronic nephritis. Hypertension	32 15	60 27	42 —	4 4	Albumin and casts Blood urea V 125 Creatinine –4.5
A. Gr. Age 32 Chronic nephritis. Hypertension Pericarditis with effusion. Died	0	25	70	20	Albumin –0 No casts Blood urea –280 Creatinine –12.0
B. R. Malignancy of prostate with retention	0	20	Nothing but mucus		Blood urea –150 mg. per 100 c.c.
O. M. Chronic nephritis Chronic myocarditis with decompensation	0	15	9	10	Blood urea –37 Creatinine –1.5 Albumin ++++ Casts and cells
M. C. Acute exacerbation of chronic nephritis with hypertension	0	22	40	4	Blood urea –64 Creatinine –2.0 Albumin ++++ Casts –
J. B. Age 34 Acute nephritis with hypertension	0	22	22	5	Blood urea –60 Creatinine –1.8 Albumin ++++ Casts Blood ++++
A. M. Age 63 Chronic nephritis with uremia and hypertension	0	35	33	27	Blood urea –150 Creatinine –3.0 Albumin –+++
Wm. Cy. Age 32 Chronic nephritis	0	7	Not enough to examine		Blood urea –80 Creatinine –2.4 Albumin ++++
M. B. Chronic nephritic	0	27			Blood urea –124

Cases for Cook County Hospital, Chicago.

higher the concentration of urea in the gastric juice. The injection of histamine in four out of five tests increased the concentration, and hence the elimination, of urea in the gastric secretion.

The ammonia content of gastric secretion of these patients with nephritis is in most instances definitely greater than normal, the normal content being rarely more than 5 mg. per 100 c.c. of juice.

DISCUSSION

In considering our results it is necessary to keep in mind the experimental method used by us to produce nephritis and that the results obtained by this method might not be comparable to conditions met with in man. Our experimental observations show a decrease in gastric secretion during the acute manifestations of nephritis, which is readily explained by vomiting (dehydration), anorexia, toxemia, and nervous inhibition due to distress. This is certainly what one would expect to occur in acute nephritis in man. But it happened that the single case of acute nephritis reported in our group of patients (Table IV) showed normal acid values in the vomitus expelled

during uremic vomiting. This possibly is an exceptional case; but it shows that at least in some cases of uremia the gastric mucosa can still form gastric juice. We cannot say to what extent; but it is probably less than normal, judging from our experimental results.

The occurrence of free acid in the continuous secretion of only three out of twelve cases of chronic nephritis, twelve hours after the last meal is

TABLE VI

SHOWING GASTRIC SECRETORY RESPONSE TO HISTAMINE AND THE AMMONIA AND UREA CONTENT OF GASTRIC SECRETION IN PATIENTS WITH NEPHRITIS

PATIENTS	BEFORE HISTAMINE					AFTER HISTAMINE					REMARKS
	AMT. IN C.C.	FREE ACID	TOTAL ACID	NH_3 MG. PER 100 C.C.	UREA MG. PER 100 C.C.	AMT. IN C.C.	FREE ACID	TOTAL ACID	NH_3 MG. PER 100 C.C.	UREA MG. PER 100 C.C.	
M.C. (1) Acute exacerabation of chronic nephritis with hypertension Blood urea –72.0 Creatinine –2.8 Albumin and casts	10	0	15	7.6	18	30*	50	65	11.2	18	Bl. Pr. 190 110
D.D. (2) Chronic diffuse nephritis with hypertension Blood urea –86.0 Creatinine –2.1 Albumin and casts Dye elim. –0	12	80	122	6.6	36	60*	137	150	2.5	43	Bl. Pr. 198 120
F.S. (3) Chronic nephritis Blood urea –225 Creatinine –4.6 Albumin and casts Dye elim. –0	6	45	70	41	17	31*	37	62	46	50	Bl. Pr. 152 76
F.S. (3) Chronic nephritis Blood urea –221 Creatinine –5.5	10 Blood Tinged	0	35	60	20	40*	42	72 Bile present +	48	46	
D.D. (2) Blood urea –96.0 Creatinine –3.7 Died three days later	20	32	70	2	4	80*	50	100	2	14	
F.S. (3) Blood urea –317.0	10	0	35	81	102	60*	25	55 Bile present	72	144	

*Sample of gastric contents 30 minutes after histamine. Stomach was not emptied. Thirty minutes continuous secretion.

unusual, since free acid is present in the continuous secretion of over 80 per cent of normal individuals. This demonstrates that there is some depression of the gastric glands in chronic nephritis as it occurs in man. However, the gastric glands in the six cases shown in Table IV were still sufficiently intact to respond to a lactose-tea meal. It is interesting to note that the three cases with edema responded to the lactose-tea meal and that in two of these the response was quite normal. We wonder if this observation might not be significantly related to the fact that any procedure that tends to produce a hydremia augments gastric secretion.

Since we have found that urea is present in small amounts in pure gastric juice of normal animals, it is not surprising to find that its concentration in gastric juice is increased by any procedure that raises its concentration in the blood.

Charcot and Canti[6] have reported that urea occurs in the vomitus of patients with nephritis. Since urea is present in saliva,[7] the significance of their observation is questioned.* Our findings on dogs with isolated pouches show without question that in nephritis we should expect and do get an increase in the urea content of gastric juice.

Our observations have an obvious bearing on what has been termed vicarious elimination[1, 8] and show that the stomach, as well as other portions of the gastrointestinal tract, must be considered as one of the eliminating organs in cases of nephritis and anuria.

The high ammonia content of the gastric juice in the patients with nephritis might come from the normal source of the ammonia in gastric secretion, which is unknown, or from bacterial decomposition of the urea in the absence of free acid, provided bacteria cannot decompose urea in the presence of free acid.

SUMMARY

1. Acute nephritis produced in dogs by occlusion of the kidney vessels for forty-five minutes decreases, but does not abolish, the gastric secretory response to a meal and to 1 mg. of histamine.

2. The chronic nephritis that follows such a procedure does not appreciably affect gastric secretion.

3. Urea (2 to 10 mg. per 100 c.c.) in small amounts has been found in the gastric secretion of most of the normal dogs studied.

4. The intravenous injection of urea causes an increase in the urea in the gastric juice; and associated with the increase in blood urea in experimental nephritis there is an increase in the urea in the gastric juice.

5. Although the gastric glands in nephritis are probably somewhat depressed as judged from the continuous secretion, it is clear from our results that they will respond to a lactose-tea meal or to an injection of histamine. We believe, however, that exceptions to this general statement may be found.

6. We have found urea in the saliva and bile free gastric juice of patients with nephritis, the urea content of the juice being high usually in those cases that had a high blood urea content.

*We have also found urea in bile.

7. We believe that these observations have a significant bearing on the rôle that so-called vicarious elimination plays in nephritis and anuria.

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METHODS FOR PREVENTING THE AGGLUTINATION OF BLOOD BY GLUCOSE SOLUTIONS*

By Walter R. Pendleton, S.B., Chicago, Ill.

I OBSERVED that glucose solutions may cause marked and prompt agglutination of human blood in vitro. I have been unable to find reference to such a phenomenon in discussions of glucose therapy, but do find that it is already known among certain laboratory men.[1] I wish to present some characteristics of the phenomenon, and to give simple methods for inhibiting or preventing its occurrence. My work has been carried out entirely in vitro and so such statements as I make are given with full realization of the need for still further investigation.

Williams and Swett[2] describe glucose reactions occurring within a few minutes to one-half hour after glucose injection and ordinarily passing off within twenty-four hours, the patient suffering from chill, fever and marked prostration. It is a question whether blood agglutination might not play a part in such a series of symptoms. Williams and Swett stated that glucose solutions become acid on autoclaving and that this might be the cause of the reaction. They found that if the P_H of the glucose solutions be brought to approximately 7.4 with a potassium phosphate buffer there would be no reaction. Ten per cent glucose solutions were used.

Stoddard[3] observed similar glucose reactions which he indicated to be by no means unusual. He stated that no further reactions occurred in the Massachusetts General Hospital during the eight months that had elapsed since they began using a sodium phosphate buffer in the glucose solutions. But other refinements were also simultaneously made in the glucose therapy. He doubted that there would be enough acid in glucose solutions to cause an acidosis reaction. Stoddard stated that 500 c.c. of the most acid solution he obtained, P_H 4.4, would probably not cause a greater drop than 0.06 in the blood P_H. His attitude is in accord with observations by Seibert[4] who

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From the Hull Physiological Laboratories, University of Chicago.

found that rabbits give no reaction on injecting 5 c.c. of sterile distilled water of P_H 4.6. Stoddard used 5 per cent glucose solutions.

Glucose solutions were prepared for the following experiments by making Merck "Pure" glucose to 50 per cent or higher concentration with distilled water. Heat was applied only for the purpose of bringing about solution of the glucose. Portions of the freshly prepared solution were diluted in distilled water as desired. Tests were made with my own blood. In each test whole blood was used immediately after leaving a skin puncture. Glucose solutions and blood were measured in the stem of a hemocytometer white cell pipette and emptied into the concave portion of a hollow ground slide. The mixture was made to the same volume in each test (about 0.016 c.c.). Air was blown through the pipette onto the drop long enough to mix the materials (2 to 3 seconds). A cover-slip was placed over the drop.

The agglutinating power of the following glucose solutions was tested: 5, 7.5, 10, 15, 20, 30, 40, 50, 80, and 100 per cent.* One part of blood was used with four parts of glucose solution. Tests showed that this volumetric ratio (of blood to glucose solution) gives roughly the maximum agglutination with solutions of varied concentrations. Solutions containing 5 to 10 per cent of glucose produced decidedly the most marked gross and microscopic agglutination. Agglutination was progressively decreased with each solution of higher concentration. There was no clumping apparent to the naked eye with the 20 per cent solution, but microscopic agglutination was very definite. The 30 per cent solution showed absolutely no gross clumping. The 40, 50, 80, and 100 per cent solutions caused a very loose microscopic agglutination. Thus approximately isotonic solutions (glucose content of 5 to 10 per cent) produced the most marked agglutination.

The next question is what occurs when a glucose solution is mixed with larger quantities of blood as would take place in the passage of the solution into the general circulation? Successive tests were made with 7.5 per cent glucose solutions using a larger proportion of blood each time. With a ratio of blood to glucose solution of 1 to 9 the corpuscles were too much separated by volume of fluid to form large agglutinated masses. Using a ratio of 1 to 4 clumps slightly less than 0.2 mm. in diameter formed. They appeared very compact under the microscope. Stirring with a teasing needle dissociated practically all clumps, but agglutination was still present microscopically. On standing clumps about 0.1 mm. in diameter reformed. With a mixture of equal parts of blood and glucose solution† the corpuscles showed absolutely no tendency to adhere to one another, but during the first minute and a half about 60 per cent of the corpuscles were crenated, for the main part without apparent shrinkage. Crenation was maximum for the series of tests at this point. With a blood to glucose solution ratio of 9 to 1, there was simply a rouleau formation of seemingly normal erythrocytes. Thus on increasing the blood content of a glucose solution in successive steps a cycle occurs in which there is (1) agglutination, (2) absence of agglutination and the appearance of marked crenation, (3) rouleau formation of apparently

*100 c.c. of solution contained 100 gm. of glucose.
†An account of intervening tests is omitted for the sake of brevity.

normal corpuscles. The 40 per cent glucose solution produced a similar cycle but in less distinct steps.

In further tests it was found that a 5 per cent solution of glucose containing 0.2 per cent sodium chloride or sodium hydroxide to N/250 strength (0.016 per cent by weight) would cause no agglutination of blood regardless of the relative amounts of the blood and glucose solutions mixed together. One-half this amount of sodium chloride or of sodium hydroxide was not sufficient to prevent agglutination. So less than one-tenth as much of the sodium hydroxide (by weight) as of the sodium chloride was required to prevent agglutination. Agglutination by a 40 per cent solution was much inhibited but not prevented by 0.2 per cent sodium chloride and N/250 strength of sodium hydroxide respectively.

Acids increased the agglutination. In each test blood was used with 7.5 per cent glucose solutions in the ratio of 1 to 4. Hydrochloric acid in N/1000 concentration seemed to cause about three times the agglutination which occurred in an unacidified glucose control. The presence of citric acid in N/50 concentration in a glucose solution converted the blood into quite firm clumps about 0.8 mm. in diameter. This was the most marked agglutination obtained in the work on glucose.

A 7.5 per cent glucose solution with N/50 citric acid content was tested with varied proportions of blood. This gave a cycle almost identical to that obtained with unacidified solutions except for the greatly increased agglutination by the acidified solution at its maximum point. It is especially noteworthy that, regardless of acid content no agglutination persisted when equal parts of blood and glucose solution were well mixed. Buffer substances in the blood would naturally here greatly diminish the activity of the acid.

Tests showed potassium acid phosphate and potassium dibasic phosphate to be antiagglutinating agents as would be expected because of their potassium content. The P_H of N/15 solutions of these salts is 4.49 and 9.18 respectively.[5] No agglutinating properties remained in 7.5 per cent glucose solutions after adding 1.0 to 1.1 per cent of potassium acid phosphate or 0.1 to 0.2 per cent of potassium dibasic phosphate. Here the dibasic salt was at least five times as effective as the monobasic salt. An N/50 concentration of citric acid necessitated the use of 1.1 to 1.2 per cent of sodium chloride or only 0.4 per cent of dibasic potassium phosphate. The buffer agent was much more efficient than sodium chloride in preventing agglutination in an acid medium but in the absence of acids its effect was about the same.

A 5 per cent glucose solution containing 0.1 per cent of oxalic acid (a sufficient amount to prevent clotting) caused a slightly greater agglutination than did the unacidified control. With 0.33 per cent of potassium oxalate in a 5 per cent glucose solution there was no agglutination.

Sucrose and glycerin solutions caused an agglutination of blood similar to that of glucose. Sodium chloride and sodium hydroxide inhibited the agglutination. Citric acid and hydrochloric acid increased agglutination. Magnesium sulphate and ammonium sulphate each prevented agglutination by sucrose solutions.

As to a possible relationship between agglutination and "glucose reactions" it might be pointed out that the solutions used by Williams and Swett

and by Stoddard, which they found to give reactions, were approximately isotonic, a concentration producing marked agglutination by our tests. The rise in acidity through autoclaving increases the tendency to agglutination. The means used by these authors in preventing the reaction (faintly alkaline phosphate buffers) will certainly inhibit agglutination in vitro. Again, Karsner and Hanzlick[6] have shown that many substances which cause anaphylactoid reactions in animals also cause agglutination of corpuscles, although they did not discuss glucose, sucrose or glycerin in this connection. Of course, if solutions be made from water infected with organisms which Seibert[4, 7] has shown to give distilled water reactions there would be an additional point of controversy in explaining solution reactions.

CONCLUSIONS

1. Agglutination of blood corpuscles by glucose solutions may be prevented by adding sodium chloride (0.1 per cent to 0.2 per cent), dibasic potassium phosphate (0.1 per cent to 0.2 per cent), acid potassium phosphate (1.0 per cent to 1.1 per cent), or by rendering the glucose solution slightly alkaline (N/250 NaOH).

2. Agglutination may be greatly diminished by the use of a definitely hypertonic solution of glucose.

3. No agglutination will persist if the glucose solution be well mixed with an equal or greater volume of blood. This can be accomplished clinically, at least in part, by a very slow injection of the glucose solution.

4. An avoidance of acid glucose solutions will diminish agglutination.

5. The agglutination phenomenon as presented here is not specific for glucose but will also occur with sucrose and glycerin.

6. Agglutination of blood or factors causing the same may possibly be responsible for "glucose reactions."

I wish to express a very sincere appreciation for the aid of Dr. A. J. Carlson under whom this work was carried out.

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LABORATORY METHODS

THE SEDIMENTATION RATE OF ERYTHROCYTES; THE CORPUSCLE VOLUME; AND THE ICTERUS INDEX*

With a Simple Method of Combining All Three Tests

By Jonathan Forman, B.A., M.D., Columbus, Ohio

THOSE of us who are engaged in making diagnostic surveys of patients, where many tests are grouped for the sake of thoroughness and the patient's convenience, find ourselves already overloaded with tests requiring a sample of the patient's blood. We present, therefore, a system of these three tests combined in one simple procedure. It has been our personal experience that, in the study of the chronic ambulatory invalid, these have been of great service.

Methods.—A 5 per cent sodium citrate solution is run into a Sahli hemoglobinometer tube up to the 30 mark. The tube is then filled up to the 100 mark with the patient's blood. The tube is inverted several times until the citrate and blood are well mixed and the mixture is allowed to stand at a warm temperature in a perpendicular position. The time is noted. Readings of the height of the red cells are made at the end of thirty minutes and one hour. Corresponding corrections of the readings are made if the plasma is found to be slightly above or below the 100 mark. It is to be noted that the readings made here are of the cell column while the European figures are for the plasma column. Upon this sedimented sample we also make a reading at the end of twenty-four hours to get the corpuscle volume, and we then use the supernatant serum, which has been diluted in an easily calculated manner, to determine the amount of bilirubin in the blood. From so simple a test then we have the following valuable information:

1. Sedimentation rate of the erythrocytes.
2. Corpuscle volume.
3. Bilirubin content of the blood.

THE SEDIMENTATION RATE

The introduction of new tests must always be done with considerable hesitancy for unless it is of decided value it will naturally be condemned. The sedimentation rate of the red blood cells, however, we have found to be of the greatest value in our own day's work. The principle upon which it rests, moreover, is not a new one. In the days of blood-letting it was observed that the red cells would agglutinate more rapidly in certain diseases

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than in others. John Hunter was the first to record this observation. In the past four years, German and Italian workers have studied the question carefully and feel that the measurement of this phenomenon gives worthwhile clinical information. In the past year, several American writers have substantiated this. The rate at which erythrocytes settle when citrated blood is allowed to stand has been used as a clinical laboratory procedure of diagnostic and prognostic worth. An increased rate is associated with pregnancy, malignancy, tuberculosis, and acute inflammatory conditions. There is the theory of Fahraeus-Hober that this increased agglutination is primarily due to a change in electrical potential between negatively charged erythrocytes and positively charged bodies in the plasma. Again there is the theory that the phenomenon is due to an increase in the fibrinogen content

TABLE I

CASE NO.	SERIAL NO.	TYPE OF CASE	READINGS		
			30 M.	60 M.	24 HR.
1	1959	Married woman, aged 56. Hypertension; constipation; acute tonsillitis; secondary anemia.	90	72	54
2	1965	Man, aged 58. Acute exacerbation of cholecystitis with stones; purpura hemorrhagica of toxic nature; secondary anemia; myocarditis.	54	37	33
3	1985	Woman, 28 years of age. Chronic cholecystitis Lane's kink; constipation; salpingitis acute.	90	70	47
4	2018	Woman, always well until 10 days ago. Gastric cancer (early); secondary anemia.	87	77	45
5	2021	Woman, aged 30, not feeling well for some time. Came for general examination which was negative. Small infection on nares, which 12 hours later was developed into typical erysipelas.	75	54	40
6	2026	Girl, 16 years old. Secondary anemia; chronic duodenal obstruction; ileal stasis; ptosis of colon.	78	65	45
7	2027	Woman, aged 60. Overweight 25 per cent; chronic cholecystitis; chronic arthritis; acute exacerbation.	91	75	50
8	2030	Woman, Afro-American, aged 50. Diabetes mellitus in extremis; marked secondary anemia.	32	29	28
9	2049	Man, 30 years old. Tuberculosis of VIII, IX, X and XI dorsal vertebrae.	85	65	44
10	2053	Man, aged 44. Lymphatic leucemia; secondary anemia.	70	60	18
11	2066	Girl, aged 5 years. Pulmonary tuberculosis.	80	64	57
12	2069	Retroperitoneal and mesenteric lymphosarcoma; ascites.	54	41	31
13	2086	Woman, aged 55. Diabetes; nephritis; gallstones with acute exacerbation.	72	61	38
14	2106	Man, aged 66. Melanosarcoma with extensive metastasis.	86	70	61
15	2107	Woman, 34 years of age. Mass at the pylorus (malignant).	88	78	44
16	2108	Man, aged 51 years. Carcinoma of the stomach.	91	79	39
17	2113	Woman, aged 58. Secondary anemia; latent jaundice; ulcer of duodenum of 13 years standing with diverticulum; chronic cholecystitis.	82	66	38
18	2122	Man, aged 34. Oral and gastric infection with organism of Vincent's angina; secondary anemia; myocarditis.	90	75	44
19	2127	Woman, aged 29. Marked secondary anemia, and pregnancy of 2 months.	88	78	38
20	2132	Woman, 35 years old. Advanced pulmonary tuberculosis.	59	39	28

of the plasma. It is also known that increase in the sedimentation rate of erythrocytes is accompanied by an increase in globulin.

As to the exact mechanism behind this test much remains to be learned. It appears, however, fairly clear that the changes occur in the plasma primarily. The various theories of how this occurs may be stated and correlated by quoting from Frosch:

"Primarily, there is a relative increase of globulin and fibrinogen in certain diseases. These particular colloids are composed of larger molecules than the other usual colloids of the blood. Thus, there is a diminution in the cohesive power between the molecules making up the plasma. Furthermore, these colloids also have a greater absorption power for the alkaline salts in the plasma and thus the negative electric charge of the red blood cells is diminished, which is conducive to more rapid agglutination of the cellular elements of the blood. Briefly, an increase in globulin and fibrinogen produces a lower surface tension of the plasma and a more rapid agglutination of the red cells, and thus a more rapid sedimentation time in those conditions in which these two colloids are increased in the plasma."

Results.—In order to conserve space only those cases with a reading below 80 at the end of an hour will be presented in the series of the first one hundred consecutive cases as they were sent to our office by their family physicians for a complete clinical, laboratory, and x-ray diagnostic study. There are twenty of these in this series.

In the second and third series of one hundred cases each, the group which fell below 80 in the first hour is of approximately the same size, viz., 22 in the second series, and 21 in the third series. In these two groups, however, we have six cases falling below 80 for which we are unable to account. These are recent cases and will be followed up to see what becomes of them.

There are several cases in which the test was of the greatest value; for instance, a man, aged sixty-two, in whom we were unable to localize a malignancy, although he presented a somewhat cachectic appearance and had a sedimentation rate of 77-59-38. We were so firmly convinced that he had a malignancy that we so reported him and asked for a chance to check up on him. In six weeks he developed difficulty in swallowing and we had no difficulty in finding a cancer of the esophagus. Again a man, aged fifty-three, presented a sedimentation rate of 97-87-42, a filling defect at the pylorus, and a four-plus Wassermann and Kahn test. Because of the pyloric obstruction and the statement of Brown that 66 per cent of cancer with evidence of gastric cancer and positive Wassermann are cases of gastric cancer, we ignored the sedimentation rate and sent this man to a surgeon. A large luetic ulcer was resected. We feel now that we would rely upon the sedimentation rate as the differential point. Again a highly neurotic man, well known to us, came with a pain in the left lower quadrant. All tests and examinations were negative except that there was general weakness, a moderate secondary anemia, a rapid sedimentation rate (69-47-20), and a spasm of the colon upon the administration of the first barium enema. This was absent at the second examination. On the strength of the evidence, an exploratory operation was advised but refused for a few weeks. He was then studied by another gastro-

enterologist who found nothing new except a further development of the secondary anemia. Upon the combined opinions, he submitted to an exploratory operation in about ten days. By this time a mass had appeared in the abdomen. He was found to have an inoperable nonobstructing cancer of the left side of the transverse colon.

Again a woman, aged forty-two, was sent to us by a surgeon to rule the gastrointestinal tract in or out of her diagnostic picture. During the past six months, she had three attacks of chills, fever, and abdominal pain, and diarrhea. Each time she had been attended in a different city and attended by a good physician. In each instance it was thought to be "intestinal flu." When she came to us the last attack had occurred during the previous week. The sedimentation rate was rapid (81-68-35). The gastrointestinal tract was negative. There was a trace of albumin and some pus cells in the urine. These facts compelled us to send her back with a diagnosis of a suppurative lesion of one or both kidneys and a request for a urologic examination. This was done and a right pyonephrosis was found.

The sedimentation rate of the erythrocytes is therefore not a specific test for any one disease but is obtainable in all conditions in which there is accompanying tissue destruction. It has been aptly compared in its use to that of the clinical thermometer. We want to urge its adoption by the internist and by the general practitioner. The internist, because he does not as a rule know his patient intimately, will be given by this test a clue within the first hour of their acquaintance as to whether the patient is the victim of any of the tissue destroying diseases. The general practitioner can employ it with profit because he may have grown deaf to the constant complaining of the neurotic patient who may in the meantime have developed some important pathology.

THE CORPUSCLE VOLUME

The reading at which the red blood cells stands at the end of twenty-four hours is taken as the corpuscle volume.

In the hemolytic anemias the volume index is increased.

Textbooks usually set forth the criteria upon which a diagnosis of pernicious anemia is based as (1) high color index, (2) poikilocytosis, (3) nucleated reds, especially megaloblasts. The variations in hemoglobin readings by different methods and different workers make it a very uncertain procedure in borderline cases unless resort is made to the more complicated analytical methods which are consuming and require too large a quantity of blood. The plus color index, found constantly if our technic is not at fault, in pernicious anemia, is due to the increase in the size of the cell. They are never supersaturated with hemoglobin. The determination of the corpuscle volume is not only more simple and therefore more apt to be correct, but it is a more basic thing and therefore should be used in the study of all anemias. The *volume index* equals $\frac{\text{volume percentage of cells.}}{\text{number percentage of cells.}}$ A plus volume index is a constant finding in pernicious anemia and is present in early cases in which other qualitative changes are not apparent.

A plus volume index together with the absence of free hydrochloric acid in the gastric juice is practically pathognomonic evidence of pernicious anemia.

In the secondary anemias, this information is of value since increase in cell volume must precede the increase in Hb content. Given two patients with low Hb, improvement is necessarily more rapid in the one having the cell volume index nearest normal.

THE ICTERUS INDEX

So far as is known, the yellow color of the blood serum in the *fasting* patient is due to the bilirubin. Increase in color can safely be taken therefore to mean increase in the bilirubin content if the precaution is observed to take the sample in the fasting state. Such increases occur in

1. Hemolytic processes in the body,

   such as
   - Pernicious anemia
   - Hemolytic jaundice
   - Hematoma
   - Rupture of a viscus
   - Malaria

2. Disturbance in the biliary system,

   such as
   - Cholangitis
   - Cholecystitis
   - Cholelithiasis
   - Adhesions about the gall bladder
   - Diseases of the liver

In dealing with the chronic ambulatory invalid with diseased gall bladder we have not found it of much value because they have come to us in the interval between attacks.

In secondary anemias we find a serum that is paler than normal as a rule.

At the end of the twenty-four-hour period, after the reading has been taken, the supernatant plasma is pipetted off and compared in a Sahli tube up to the 10 mark with a standard solution of 1:10,000 potassium bichromate. The number of times that the plasma must be diluted to correspond in color with the standard is taken as the *icterus index*. The normal range is from 4 to 6. It has been found that clinical jaundice is always present when the index is above 15, and invariably absent when it is below. The zone of latent jaundice lies, therefore, between 6 and 16.

Latent jaundice is an important bit of information—

1. The prediction of a toxic icterus in
   - Pneumonia
   - Exophthalmic goiter
   - Toxemias of pregnancy
   - Following administration of
     a) Chloroform
     b) Arsphenamine

It has recently been said that this test should be used always in connection with antiluetic therapy as it is even more important than the Wassermann.

2. The detection of passive congestion of the liver due to myocardial failure in

   Heart disease
   Emphysema
   Arteriosclerosis

3. In differentiation of primary and secondary anemias. (Normal values are the rule in nonhemolytic anemias.)
4. Involvement of liver and biliary passages in the presence of a carcinoma.
5. The differential diagnosis of cases of abdominal colic. Following biliary colic the serum bilirubin is elevated, although in about 60 per cent of cases not to a degree or for a length of time sufficient to color the sclera or skin. Here the detection of a latent jaundice is of great value.

The icterus index is therefore of considerable practical value. It is of value in giving quantitative information as to the amount of biliary dysfunction and is at present the best single functional test of the liver available. It can be done easily and readily in the office. It is also of value in the differentiation of the primary from the secondary anemias.

SUMMARY

A simple method of combining the determination of the sedimentation rate of the erythrocytes, the corpuscle volume, and the icterus index has been presented. These tests, when done in this manner, give a great deal of worthwhile information which we should dislike very much to do without in our studies of the chronic ambulatory invalid.

A RUBBER MASK FOR DETERMINATION OF OXYGEN CONSUMPTION OF THE DOG*

By Alfred Blalock, M.D., Nashville, Tenn.

IN STUDIES upon the cardiac output of the dog, a great deal of difficulty was encountered in obtaining accurate determinations of the oxygen consumption due to inability to effect an air-tight connection between the animal's mouth and the spirometer. Many methods were tried in attempts to overcome this difficulty, but none were entirely satisfactory. The most successful method consisted of the use of a mask which was made of plaster of Paris, but it was necessary that each animal have an individual one which was shaped according to the contour of the face. The mask was then covered with paraffin, and plastacene was employed to make a good connection between the animal and the spirometer. In addition to the fact that leaks were

*From the Department of Surgery of the Vanderbilt University.
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encountered rather frequently, it was unsatisfactory because it required the constant attention of one person in order to hold it in place.

Following the suggestion of Dr. Beverly Douglas, a specially constructed mask was ordered from The Baumann Rubber Company of New Haven, Conn. It is made of rather easily pliable rubber and has the shape of a funnel. The diameter of the smaller end is such as to permit of an air-tight connection with a Benedict spirometer. The larger opening is of sufficient size to allow its being placed over the animal's mouth without undue stretching. This, in turn, is surrounded by a separate hollow rubber tube which can be inflated through a smaller rubber tube leading off from the side. Before applying

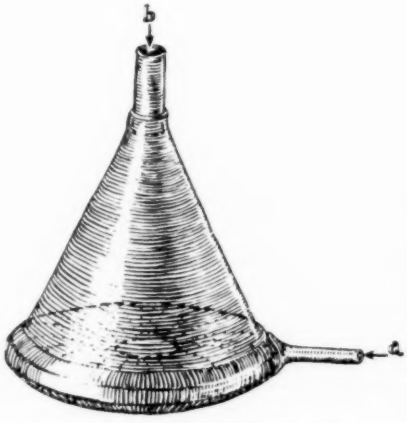

Fig. 1.—Lateral view of mask.

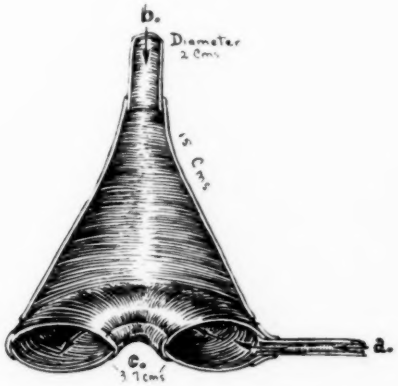

Fig. 2.—Hemisection view of mask.

the mask, the corners of the animal's mouth are anchored in place by several turns of a circular rubber dam. The mask is then placed over the rubber dam, the circular tube is inflated tightly, and an air-tight connection secured. It is very important that the circular rubber dam should not be applied too closely to the tip of the animal's nose, as this would result in respiratory obstruction.

This method has been used in at least two hundred determinations of the oxygen consumption of dogs varying in weight from five to eighteen kilograms, and no difficulty has been encountered. In addition to the accuracy which it insures, it usually allows the observer to continue with the experiment, since it is not necessary to hold the mask in place. The amount of dead space is almost negligible.

THE GLUCOSE TOLERANCE TEST*

By W. B. Lewis, M.D., Battle Creek, Mich.†

THE glucose tolerance test is daily coming to have a greater significance. It is of particular value in those early borderline conditions where diagnosis is not clear-cut and easy. Richter[1] has well said in regard to gallstone disease that "it is not gallstone disease at all on which we should focus our attention, *but the antecedent condition* of which gallstone disease is only a late complication." And likewise, in disturbances of carbohydrate metabolism it is not the well-developed condition of diabetes that we should be most interested in, but those early changes before the damage becomes great.

Several methods for detecting the prediabetic state have been proposed. In 1914, Peter Bergell[2] of Berlin, stated that the urine of a prediabetic free of sugar had a greater solvent power for cupric hydroxide than normal urine. We have used this test extensively. A report of this work will appear later. Concerning some cases, it gave early and valuable information. In many others it did not.

In 1918, S. R. Benedict[3] proposed his sodium picrate method for normal sugar in the urine, and on the basis of results with this method he drew the conclusion, "If the total sugar elimination amounts to more than one and a half grams per day, the diet should be altered until this figure is reached as the upper limit."

In 1922, Folin and Berglund[4] adapted the Folin and Wu[5] blood-sugar method to the determination of the normal sugar in the urine and published their classical research on carbohydrate metabolism. Their normal sugar method was not proposed as a prediabetic test, but rather the contrary; it showed that *the reducing substances of normal urine are mainly not dextrose but*, "First, foreign, unusable, carbohydrate materials present in grains, vegetables and fruits; and second, decomposition products due to cooking, canning and baking of such food. The sugar of normal urine consists, therefore, of a motley variety of carbohydrate products and carbohydrate derivatives, including di- and polysaccharides." Therefore, the elimination of one or two grams of such substances per twenty-four hours is not an indication of the prediabetic state but dependent almost entirely on the diet.

It is the use of this method of Folin and Berglund for the study of the urine in conjunction with blood-sugar curves following the ingestion of dextrose that we believe gives one the most reliable information regarding early disturbances of carbohydrate metabolism.

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†From the Clinical Laboratories of the Battle Creek Sanitarium.

METHOD

1. At 7:00 A.M., patient empties the bladder and drinks one glass of water.

2. At 8:00 A.M., one-hour specimens of urine and fasting blood sugar are obtained. Patient is then given 100 gm. of pure dextrose dissolved in water with the juice of one lemon and made up to 200 c.c., also one glass of water.

3. At 8:30 A.M., blood and urine specimens are obtained.

4. At 9:00, 10:00, 11:00 and 12:00 o'clock, blood and urine specimens are collected.

Blood sugar is determined by the Folin and Wu method. Each urine specimen is tested for sugar, first qualitatively with the Folin-McEllroy[6] reagent. Then, on the basis of the amount of reduction obtained, the urine is diluted and the sugar determined quantitatively by the Folin-Berglund normal sugar method. By the use of tables the dilutions and calculations are relatively simple. Urinary sugar is expressed as milligrams per hour.

RESULTS

TABLE I

TYPICAL RESULTS SELECTED FROM 600 CASES

NAME		FASTING	½ HOUR	1 HOUR	2 HOUR	3 HOUR	4 HOUR	
Mr. M. H.	Blood Sugar	83	132	125	96	78	83	Normal
	Urinary Sugar	25	6	9	18	15	18	
Mr. L. S.	Blood Sugar	80	143	133	83	74	83	"
	Urinary Sugar	10	7	13	23	20	15	
Mr. D. H.	Blood Sugar	83	106	86	88	81	66	"
	Urinary Sugar	16	7	9	14	12	8	
Miss G. E.	Blood Sugar	76	95	104	81	86	82	"
	Urinary Sugar	28	5	8	21	10	9	
Miss R. K.	Blood Sugar	91	105	85	70	65	83	"
	Urinary Sugar	21	13	8	10	12	10	
Dr. W. F. M.	Blood Sugar	111	167	—	182	120	—	Slight
	Urinary Sugar	9	89	—	99	372	—	disturbance
Mr. P. R.	Blood Sugar	83	167	91	79	56	91	"
	Urinary Sugar	13	13	60	22	15	14	
Mr. L. K.	Blood Sugar	106	194	208	204	114	95	"
	Urinary Sugar	5	37	1072	2240	1144	1318	
Four months	Blood Sugar	77	159	159	159	100	53	"
later	Urinary Sugar	8	13	60	201	35	13	
Mrs. L. G.	Blood Sugar	106	194	187	220	200	103	"
	Urinary Sugar	26	13	119	633	759	118	
Mr. E. C. M.	Blood Sugar	130	240	316	273	192	130	Moderate
	Urinary Sugar	33	423	1753	1715	1177	160	disturbance
Mrs. G. F.	Blood Sugar	133	217	345	370	192	128	"
	Urinary Sugar	14	12	450	4381	1444	110	
Mr. W. B. C.	Blood Sugar	154	286	364	333	250	157	"
	Urinary Sugar	29	240	2562	6256	4347	940	
Mrs. K. H.	Blood Sugar	164	313	364	351	278	149	"
	Urinary Sugar	67	77	3068	8765	7443	2234	
Mrs. K. B.	Blood Sugar	182	286	333	308	308	222	"
	Urinary Sugar	18	11	220	1068	2200	80	
Miss M. S.	Blood Sugar	182	333	400	400	286	211	Severe
	Urinary Sugar	14	353	6400	9325	5265	952	disturbance
Mr. M. D.	Blood Sugar	200	357	435	465	351	270	"
	Urinary Sugar	—	735	4620	13000	11714	6912	
Mr. H. S.	Blood Sugar	213	263	364	417	377	286	"
	Urinary Sugar	13	11	423	4615	8000	3352	
Mr. S. H.	Blood Sugar	215	364	370	377	299	241	"
	Urinary Sugar	1800	3000	5683	16156	8800	4596	

Fig. 1. Normal. These curves are typical of over 100 obtained from students and others. Fasting blood sugar of 80 to 100, rising to a maximum at one-half hour, usually less than 150; then rapidly falling, usually below the starting point at the second or third hour and then rising to near the starting point.

The urinary sugar when expressed in mg. per hour forms a curve that corresponds closely with the blood-sugar curve. In this normal it is 10, 9, 10, 16, 18, and 15 mg. per hour, relatively very constant. *It is this close paral-*

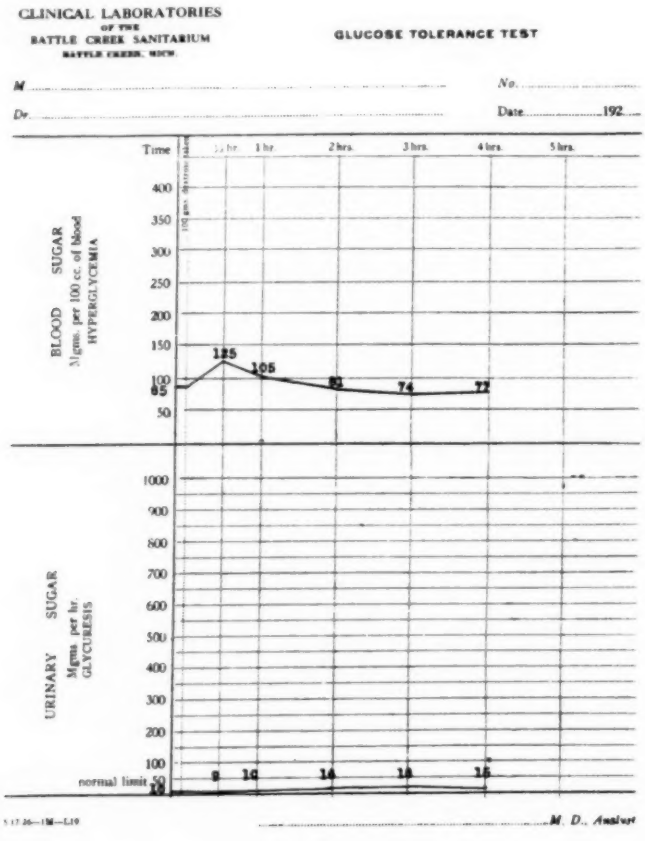

Fig. 1.

leling of the urinary sugar curve with the blood-sugar curve that I wish to call special attention to.

Fig. 2. Slight disturbance. In this case the patient had had a long siege of boils for over a year without making any progress in getting rid of them. The fasting blood sugar is 111 and rises to a maximum of 182 at the second hour and at the third is still above the starting point. The urinary sugar closely follows this; starting at 9 mg. per hour it rises to 372 at the third hour. Following the test he markedly lowered the carbohydrates in his diet, and in three weeks the boils had disappeared and have not returned in nearly a year.

Fig. 3. Moderately severe disturbance. This is an interesting case, showing the diagnostic value of the test. A fasting blood sugar of only 135 and no increase of sugar in the urine. Her main complaint was that of easily tiring and weakness. Had no suspicion of diabetes. At one hour the blood sugar reached a maximum of 333 and at three hours was still 174. The urinary sugar curve is very similar, showing at the second hour a maximum of 6.6 gm.

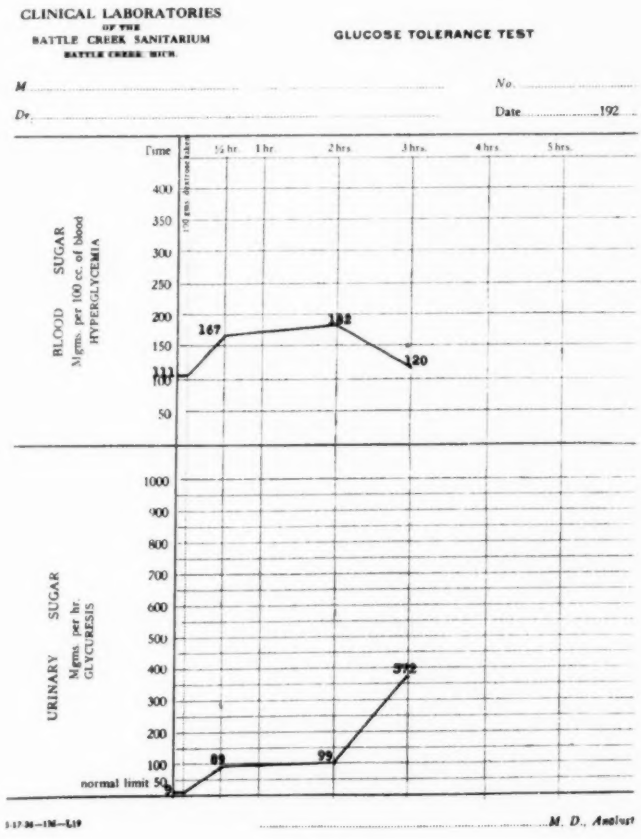

Fig. 2.

Fig. 4. Severe disturbance. This patient also had not been diagnosed as a diabetic, although the fasting blood sugar was 213. There was a high renal threshold as there was no increase above normal of the urinary sugar. A typical diabetic blood-sugar curve which at the end of four hours is still 286, with large amounts of sugar in the urine.

DISCUSSION

1. Our results confirm Folin's in showing that there is a very definite renal threshold for dextrose.

Until the renal threshold is passed, the amount of reducing substances in the urine is relatively very constant.

The average healthy individual does not exceed this threshold and there is, therefore, no increase of normal sugar in the urine above 40 or 50 mg. per hour as a maximum after taking 100 gm. of dextrose. We, therefore, have adopted this figure as our maximum normal limit.

2. Practically all of our cases showing a fasting blood sugar of 130 or more, by the tolerance test, showed some degree of disturbance of carbohydrate metabolism. Therefore, a fasting blood sugar of 130 should be looked upon with grave suspicion.

3. But, what is even more important from the diagnostic standpoint is

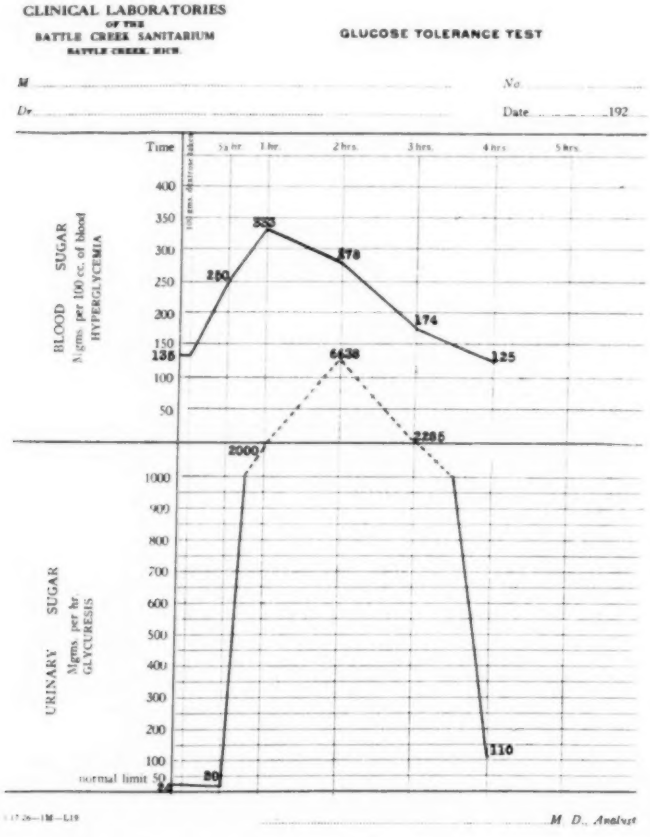

Fig. 3.

the large number below 130 blood sugar that show disturbances of carbohydrate metabolism of varying degree, some quite severe. Approximately 32 per cent of our series of 600 on *sick people*.

A fasting blood sugar within the usually accepted normal limits is therefore no guarantee that disturbances of carbohydrate metabolism are not present when the organism is subjected to a slight strain, as in the tolerance test.

4. Because of the need of more frequent testing of carbohydrate metabolism, I would suggest, based on the results in this series, the following as

a preliminary test that may be carried out by any physician: Give the patient 100 gm. of dextrose with instructions to save the urine for one hour previous to taking it, in the morning, without breakfast, and for four hours following, in hourly periods. Have the patient bring these specimens to the physician's office where he will run a qualitative sugar test on each, and from this he will get a very good idea whether any abnormality is present. If there is, then have a laboratory equipped for blood chemistry do a complete tolerance test.

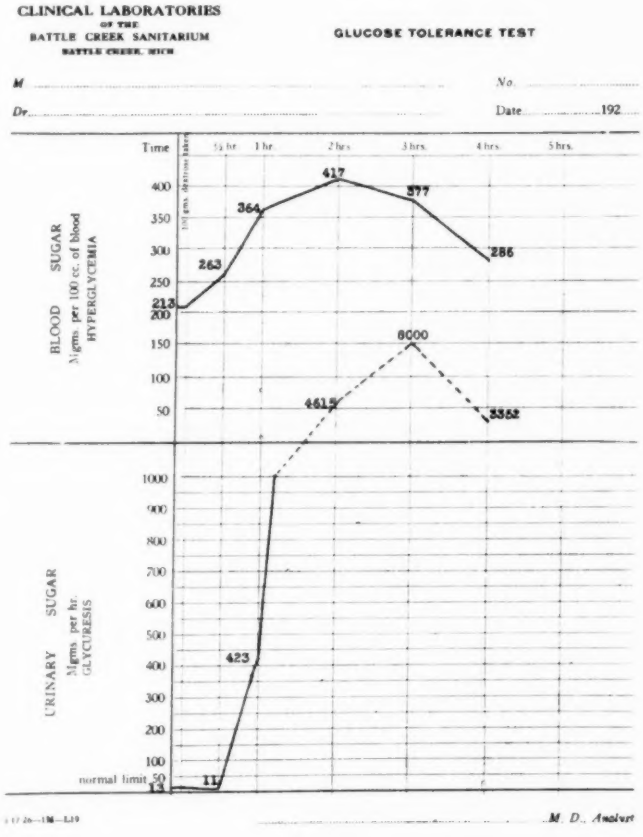

Fig. 4.

5. In this series the test was found of value in the following conditions:

1. Diabetes mellitus.
2. Renal diabetes.
3. Hyperthyroidism.
4. Furunculosis.
5. Pruritus.
6. Testing the susceptibility of near relatives of diabetics.
7. Pituitary disturbances.
8. Hypoadrenalism.
9. Arthritis.

10. Organic and functional nervous diseases.
11. Vagatonia. We get a very characteristic curve in this condition. The condition has not been very generally recognized and relatively few cases are reported in the literature. In collaboration with Dr. M. J. Nielsen, of the neurologic department, such a group is being studied and a report of this will appear soon.

SUMMARY

1. A combination method of blood sugar and normal sugar in the urine is described.

2. Normal sugar in the urine is quite constant when expressed in milligrams per hour.

3. Some individuals with a normal fasting blood sugar show a disturbed carbohydrate metabolism.

4. Individuals with a fasting blood sugar of 130 or more nearly always show disturbed carbohydrate metabolism.

5. Various diseases and conditions in which a dextrose tolerance test is indicated are mentioned.

6. A simplified preliminary test for more general use is advocated.

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DISCUSSION

Dr. Carl Spohr.—I would like to ask whether Dr. Lewis makes any variation in the amount of glucose administered.

Dr. Wm. G. Exton.—It would be better if it were standardized. If we could get our data together in the same terms it would mean more.

Dr. A. H. Sanford.—The standardizing of the administration of glucose reminds me of something that Dr. Wilder suggested, and never tried, to my knowledge. There is a little difficulty in getting a patient to swallow a solution of glucose. We could make up the required amount of glucose in the form of stick candy; this would be a pleasant form for its administration.

Dr. F. W. Hartman.—The whole question of the glucose tolerance test is involved and the curves are difficult to interpret even when based on blood examinations. As I understand Dr. Lewis, his curves are based on urine examinations, and this we believe would make the curve still more difficult to diagnose especially since the kidney after a time builds up a tolerance to glucose and we may get values in the blood as high as 400 mg. per 100 c.c. before any appears in the urine.

Dr. W. B. Lewis (closing).—I was very much interested in Dr. Exton's remarks. Any procedure of this kind should be standardized; that is, normals established with the technic described, and the interpretation based on these results. It makes the interpretation of the results more uniform.

Intravenous administration, as mentioned by Dr. Hartman, may give us more accurate results, although after giving the glucose by mouth in a large number of cases the results have been very uniform and satisfactory. Certainly it is more easily carried out and lessens the possible objections to more frequently performing the test.

In regard to the amount of glucose administered. After having tried the test on a large number of students, I believe the variations of the curve due to weight are slight. It therefore adds to the simplicity of the test to always give 100 gm., and if quite commonly adopted would be a step in standardizing the test as suggested by Dr. Exton.

A MODIFIED DIGESTION ACID FOR NONPROTEIN NITROGEN DETERMINATION*

By Martin Dupray, B.S., M.S., Hutchinson, Kansas

SEVERAL digestion mixtures have been suggested for total nonprotein nitrogen determinations in blood. That of Folin and Wu[1] is probably the best known and most used. The only fault of their mixture is the tendency to form precipitates in the cooled digest. Part of this precipitate (silica) is insoluble in water and sometimes causes trouble in color comparison because of turbidity.

I have found that perchloric acid[2] may be added to sulphuric acid, giving a very efficient digestion acid that does not form a precipitate on cooling. It is prepared as follows:

Fifty c.c. of distilled water are placed in a small flask, and 46 c.c. of sulphuric acid, nitrogen free, specific gravity 1.84, are added slowly while stirring. The mixture is cooled. Then 2 c.c. of perchloric acid, 60 per cent, and 2 c.c. of phosphoric acid, 85 per cent, are added and the solution mixed and transferred to a glass-stoppered bottle. The phosphoric acid is added to prevent a precipitate of WO_3 in blood filtrates prepared by the tungstic acid method of Folin and Wu. The solution keeps indefinitely.

One c.c. of the above digestion mixture is used for 5 c.c. of blood filtrate in the method of Folin and Wu. The digestion is carried out as in the Folin and Wu method. The digestion is a little more rapid than with the Folin and Wu digestion acid. The digest will often not be completely colorless when hot, but will retain a slight lemon yellowish tinge due to chlorine. This color is readily distinguished from the yellowish brown color due to the last traces of undestroyed organic matter. The faint yellowish color rapidly fades on cooling, leaving a clear colorless solution. No precipitate forms on cooling and the digest may be cooled to room temperature before adding water. The test is carried out otherwise as in the Folin and Wu technic. It may be nesslerized direct, or the ammonia may be aspirated or distilled off as desired.

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[2]For the use of perchloric acid in macrokjeldahls see Mears, B., and Hussey, R. E., Jour. Ind. and Eng. Chem., 1921, xiii, 1054.

*From the Dupray Laboratory, Hutchinson, Kansas.
Received for publication, September 28, 1926.

OXYGEN THERAPY. A METHOD OF ADMINISTRATION AND APPARATUS*

By Paul Roth, M.D., Battle Creek, Mich.

OXYGEN therapy is indicated primarily for the relief of anoxemia and various disturbances to which it leads. The seriousness of the effects of oxygen want has been appreciated only in recent years and the clinician in general still needs to be awakened to the advantages and effectiveness of the more modern and improved methods of oxygen administration.

The surprisingly slow progress made in the therapeutic uses of oxygen from which so much has been justly expected ever since that element was discovered, is due, as well stated by Haldane[1] to: (1) "Failure to understand both the immediate and the remote effects of oxygen want." (2) "Failure to appreciate that the longer the period of want of oxygen lasts, the greater is the progressive damage done to the central nervous system, heart, and other organs and the slower and more difficult does recovery become. A deficient oxygen supply to the body, if allowed to continue, is undoubtedly a matter of very serious moment to a patient, and should be prevented, if this is at all possible." Haldane further says: "Anoxemia is not only always dangerous, but its injurious effects may soon become irreparable though the anoxemia may have been effectively corrected."

When this was written, seven years ago, this author remarked: "It seems evident that there is a wide field for the therapeutic use of oxygen, and probably oxygen will before long become one of the commonest remedies." Today oxygen is, as yet, anything but a common remedy in spite of its having been for years a very common article obtainable at a relatively low cost.

It is hoped that every clinician now knows that the feeding of oxygen in whiffs from a rubber bag or from a tank, is obsolete and, with but rare exceptions, useless. In most cases it should be administered by the hour or half hour at least, more or less frequently repeated, and often as continuously as possible.

The possibility of obtaining in certain cases definite results from even shorter periods of administration must not be disregarded. For instance, H. Simon[2] reports that in six of ten cases with nephritic and arteriosclerotic hypertension, a permanent lowering of the blood pressure was obtained as the result of inhaling for six to eight minutes, several times a day usually, about six liters of oxygen per minute.

The ideal method of oxygen therapy is by means of a specially built room, the atmosphere of which is mechanically regulated to contain from 30

*Abstracted from paper read before the Fifth Annual Convention of the American Society of Clinical Pathologists at Dallas, Texas, April 15, 16 and 17, 1926.

From the Research and Metabolism Laboratories of the Battle Creek Sanitarium.

to 60 per cent of oxygen with no excessive amount of CO_2 or moisture and maintained at a desirable temperature at all seasons of the year. Such facilities are necessarily elaborate, costly to install and to operate. Fortunately excellent results are obtainable by less elaborate equipments.

The simple methods of oxygen feeding by means of a mask, mouthpiece, or nasal tube, while suitable for short periods, as in emergency work, have generally been found to seriously interfere with the comfort of the patient. Nevertheless, such means will never be entirely ignored in the absence of better ones. Attention should be called to the fact that there are now scattered all over the land a large number of respiration apparatuses for the estimation of the basal metabolic rate. Without any modification they are very suitable oxygen feeders, though they require much attention when used for this purpose.

The comfort of the patient must be considered as well as the efficiency of the method of administration, therefore, any contrivance which interferes with the movements of the patient, especially of the head, are objectionable because they invariably become intolerable in prolonged use.

The bed tent described by Hill and also by Barach and Binger has been reported to be very practical and efficient. The chief disadvantage of the full bed tent is that it does not allow free access to the patient to tender usual nursing care and treatment, without suspending the oxygen feeding. It is also more cumbersome and wasteful of the oxygen required to maintain an adequate concentration.

The hood or head tent proposed by the writer and previously described[3] has continued to give entire satisfaction. The skirt of this hood is made fuller at the lower part making it possible to enclose the head, shoulders and arms, if desired. Fig. 2.

Analyses have shown that with a subject weighing 70 kg. a flow of oxygen of 3, 4, 5, 6, or 7 liters per minute will maintain in the hood approximately and respectively 30, 40, 50, 60, or 70 per cent of oxygen. Immediately after the hood is properly adjusted, oxygen is freely admitted in the apparatus for about one minute. The flow is then reduced to that necessary to maintain from 40 to 50 per cent concentration of oxygen in the air inhaled by the patient. Barach has confirmed the fact that concentrations of oxygen exceeding 70 per cent become harmful when breathed for a long period of time.[4]

The administration of oxygen in a hood or tent enclosing the head only, or also the shoulders and arms, presents the following distinct advantages:

The comfort of the patient is not interfered with because the movements of the body or of the head are not restricted by mouth or nasal connections or the use of a mask.

The administration of oxygen at any desirable concentration is easily secured and uniformly maintained, chiefly because it is relatively easier to keep well ventilated a small hood than a tent covering the entire bed, or a larger enclosure of any kind.

The patient is readily accessible at all times for general care and treatment, which can be administered without interfering with the oxygen feeding.

The air and oxygen supply is readily maintained pure and sweet. The fouling by gases from the bowels, or by other noxious emanations from the body surface, increased often by the application of compresses, fomentations, packs, diathermy or of dressings and ointments, is avoided.

The hood can also be more easily kept comfortably cool, thereby securing the distinct therapeutic advantages of cold air, which is a valuable respiratory and cardiac tonic. At the same time the patient can be cared for in a properly heated room, thus avoiding the dangers of exposure to cold.

This method of administration has proved to be efficient while the cost of operation is minimized. Such a simple and transportable equipment as the one here described can readily be installed at the residence of the patient. The

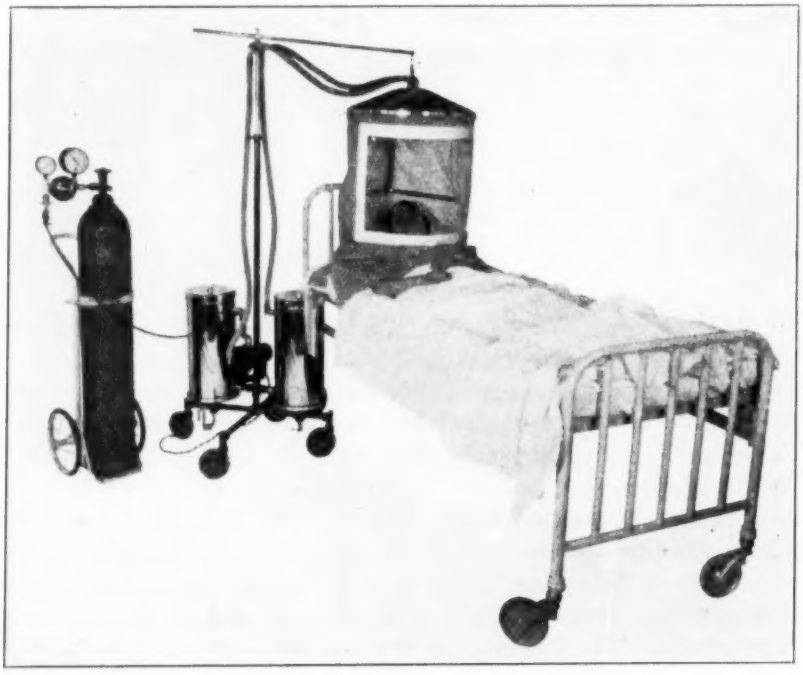

Fig. 1.

demand for such facilities already exists in practically every hospital and medical institution.

The introduction and operation of an equipment for oxygen therapy demands intelligent supervision. For plausible reasons, the clinical pathologist will probably be more often consulted than anyone else and his expert cooperation enlisted for this purpose.

It is safe to predict that oxygen therapy, properly conducted in its legitimate field of usefulness, will save more lives than resuscitation apparatus have or ever will in emergency work.

This oxygen therapy outfit (Fig. 1) is a reconstruction of the apparatus previously described.[3] The purpose of the builder* was to dispense with the

*Warren E. Collins, 555 Huntington Ave., Boston, Mass.

use of the cabinet and group the various parts into a more compact and more easily transported unit. He also devised for this apparatus a remarkably efficient and quiet-running ventilator operated by a universal motor.

To the left of this ventilator is the air cooler which is filled with pieces of ice the size of one or two fists, over which the air passes directly instead of through metal coils. This method of air refrigeration was suggested by Dr. Alvan L. Barach.[4] A U-shaped trap drains the cooler. The other large can on the right contains the soda lime for CO_2 absorption.

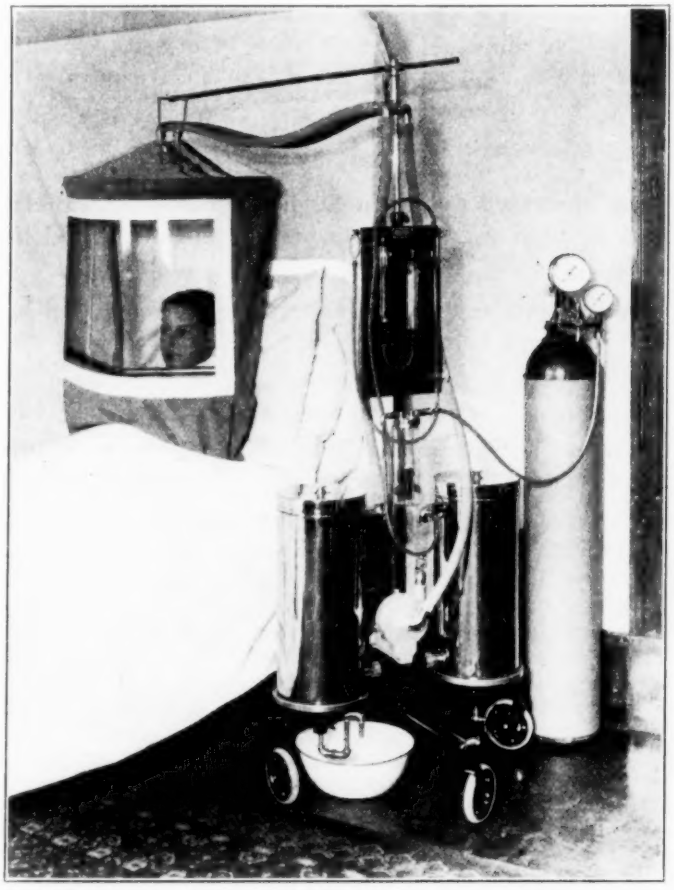

Fig. 2.

The flow of oxygen is measured by means of a special "Oxweld" reducing valve which indicates on the smaller dial the flow in liters per minute. The wash bottle type of flow meter previously described[3] is also shown in Fig. 2. This will answer the purpose with the use of any ordinary reducing valve.

Barach also advised to admit the fresh air in the hood through the perforated tube formerly used to remove the expired air. The fresh cool air is thus blown directly toward the face. While this presents an advantageous feature, the writer believes that the ideal position for the perforated de-

livery tube is, as shown in Fig. 1, above and behind the head of the patient. It is there out of the way, does not obstruct the view through the large single celluloid window and facilitates the handling of the hood preparatory to or during treatment. Besides, if the fresh air is introduced from the rear it will not meet the intermittent current of expired air coming from an opposite direction, mixing with it more or less and reducing its oxygen concentration before it can be inhaled. The expired air will thus be more readily carried away from the vicinity of the nose or mouth and, being warm, will tend to rise toward its outlet at the top of the hood.

Fig. 2 shows above, mounted on a board, the very simple apparatus described by Binger[5] for the rapid determination of oxygen. With it the concentration of oxygen in the inspired air in the hood can readily be ascertained as frequently as necessary.

SUMMARY

1. Deficiency of oxygen supply in the living tissues soon results in grave disturbances, which often are more easily prevented than relieved.

2. Oxygen should become one of the commonest remedies.

3. The advantages of oxygen administration in a small tent or hood, enclosing the head only, are discussed.

4. This method permits the administration of oxygen in combination with the therapeutic use of cold air in a properly heated room.

5. The apparatus can quickly be installed in any home as well as at the hospital and operated from an ordinary electric light socket.

6. Several additional improvements in the apparatus are presented.

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[4]Barach, A. L.: The Effect of the Inhalation of Oxygen Over Long Periods of Time in Normal Rabbits and in Rabbits with Pulmonary Tuberculosis, Am. Rev. Tuberc., April, 1926, xiii, 293.

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DEPARTMENT OF REVIEWS AND ABSTRACTS

ROBERT A. KILDUFFE, M.D., ABSTRACT EDITOR

Kendall, A. I., and Keith, H. R.: Nature of the Soluble Proteolytic Enzyme of B. Proteus. Jour. Infect. Dis., March 3, 1926, xxxviii, No. 3, 193.

A report of a quantitative study of the changes induced in gelatin by the soluble enzyme of B. proteus. The proteolytic enzyme of this organism produces a rapid change in the gelatin molecule of the tryptic rather than peptic type, the rate and extent being equal or even greater than that of commercial trypsin under parallel conditions.

Study of the flora of nurslings (Kendall, A. I., Day, A. A., and Walker, A. W.: Chemistry of the Intestinal Flora of Nurslings. Jour. Infect. Dis., March, 1926, xxxviii, No. 3, 200), indicate that the nitrogenous changes induced by bacteria are slight. Proteolysis of bacterial origin is minimal. The striking change is a pronounced utilization of glucose and lactose, principally the latter.

In artificially fed infants (Kendall, A. I., Day, A. A., and Walker, A. W.: Chemistry of the Intestinal Bacteria of Artificially Fed Infants. Jour. Infect. Dis., March, 1926, xxxviii, No. 3, 205), the feces induce putrefactive changes in sugar-free mediums and fermentative changes when carbohydrates are added.

In adults (Kendall, A. I., Day, A. A., and Walker, A. W.: Chemistry of the Intestinal Flora of Normal Adults. Jour. Biol. Chem., March, 1926, xxxviii, No. 3, 211), the chemical picture is one of unexpected uniformity in the nitrogenous changes.

Moderate proteolysis occurs in mediums containing no utilizable carbohydrate which is nearly entirely suppressed when carbohydrates are added.

When the intestinal flora contains B. aerogenes capsulatus there is marked proteolysis.

When abnormal numbers of gas bacilli are present (Kendall, A. I., Day, A. A., and Walker, A. W.: Chemistry of the Intestinal Flora of Man Containing Abnormal Numbers of Gas Bacilli. Jour. Infect. Dis., March, 1926, xxxviii, No. 3, 217), the outstanding feature is marked proteolysis accompanied by extensive deaminization resulting in the accumulation of ammonia in the culture.

In carbohydrate-containing mediums these activities are almost entirely suppressed.

The influence of insulin upon the utilization of glucose in the diabetic suggested the study of its possible effect on nonglucose-fermenting bacteria (Kendall, A. I.: Nonglucose-Fermenting Bacteria and Insulin. Jour. Infect. Dis., October, 1925, xxxvii, No. 4, 329), with entirely negative results.

The results of the adding insulin to milk-glucose-insulin cultures of B. bulgaricus and B. acidophilus, as shown by detectable increase in titratable acidity, were indefinite and remain an open question (Kendall, A. I., and Ishikawa, M.: Effect of Insulin on Cultures of B. Bulgaricus and B. Acidophilus. Jour. Infect. Dis., October, 1925, xxxvii, No. 4, 333).

Peters, J. B., Bulger, H. A., Eisenman, A. J., and Lee, C.: Concentration of Acids and Base in Normal Plasma. Jour. Biol. Chem., January, 1926, lxvii, No. 1, 141.

With the primary purpose of obtaining an insight into the mechanism of the changes in the blood and tissue hydration in nephritis, the authors report an intensive study of three years' duration.

In all cases chloride and bicarbonate, and in most cases the proteins of the plasma were determined. Additional studies were added as they seemed indicated.

This, the first of a series of papers, describes in detail and at length the experimental methods and technic employed and these cannot well be abstracted without almost a transcription of the entire paper.

From a study of normal individuals the following conclusions were formulated:

The total base, inorganic acids, bicarbonate, chloride, phosphate, and protein were determined.

The difference between total base and the sum of the base-combining powers of the acids enumerated gives a measure of the organic acid and sulphate. The latter is present in negligible amounts only so the "undetermined" acid must be practically equivalent to organic acid.

Normal serum contains 147 to 161 millimols of monovalent base, 138 to 148 millimols of this base being combined with the four acids, protein, bicarbonate, chloride, and phosphate. For hospital patients these limits should probably be extended to 145 to 167 for total base and 135 to 155 for total acid. The organic acid never exceeded 20 millimols in normal persons.

There is a general tendency for protein, bicarbonate, and chloride to reciprocate in their changes in the maintenance of a constant level of acid and total base.

When the CO_2 tension is increased from 30 to 60 mm. at 38° C. (II, Eisenman, A. J., Bulger, H. A., and Peters, J. P.: The Effect of CO_2 Tension on the Concentration of the Acids of the Plasma of Oxygenated Blood. Jour. Biol. Chem., January, 1926, lxvii, No. 1, 159), the sum of the base-combining powers of the acids HCO_3 plus Cl plus protein of the plasma of oxygenated blood increases about 2 millimols. In this change HCO_3 increases 5 millimols, the extent being determined chiefly by the hemoglobin concentration or volume of the blood cells. The average change of plasma volume amounts to −0.6 volumes per cent while the base-combining power of the proteins diminishes about 0.8 mm.

Cl decreases by about 2 millimols. Because base does not traverse the cell membrane the loss of water from plasma to cells results in a concentration of base that neutralizes the excess acid.

The general conception that arterial and venous blood differ as regards electrolyte equilibria only in so far as they contain more or less carbon dioxide and oxygen is erroneous (Peters, J. P., Bulger, H. A., and Eisenman, A. J.: III, The Differences Between Arterial and Venous Blood. Jour. Biol. Chem., January, 1926, lxvii, No. 1, 165).

Arterial and venous blood may contain also different amounts of water and chloride and the carbon dioxide absorption curves may also differ. The changes that occur while the blood is traversing the tissues affect the different components to different degrees and in different directions for reasons not yet determined.

The end-result on the plasma acids is an average alteration of 2.5 millimols, usually an increase. The maximum variations encountered were +5 and −2.5 millimols.

Venous obstruction leads to a transfer of water from the blood to the tissues and a concentration of the proteins (Peters, J. P., Bulger, H. A., Eisenman, A. J., and Lee, C.: IV, The Effect of Stasis, Exercise, Hyperpnea, and Anoxemia; and the Causes of Tetany. Jour. Biol. Chem., January, 1926, lxvii, No. 1, 175). In brief, vigorous exercise, considerable lactic acid and an excess of carbonic acid are formed and the serum P_H falls. Chloride remains unchanged. Bicarbonate cedes some base to the organic acid, but the major portion of the latter is neutralized by base yielded from the tissues.

If over-ventilation is produced rapidly symptoms of tetany appear when the P_H has risen not more than 0.2. Although the total CO_2 falls, the CO_2 capacity is unaltered.

Organic acid is considerably increased. The base required for neutralization of foreign acids is largely derived from the chlorides, which are diminished.

The reaction of electrolytes to oxygen-want varies according to the respiratory response.

Any given disturbance of electrolyte equilibrium evokes a train of reactions in all the other electrolytes tending to restore equilibrium.

Studies in various pathologic conditions are reported (Peters, J. P., Bulger, H. A., Eisenman, A. J., and Lee, C.: V, Miscellaneous Pathologic Conditions. Jour. Biol. Chem., January, 1926, lxvii, No. 1, 219).

The effects of vomiting are highly variable and probably depend on the nature of the vomitus, the severity and duration of the emesis, and the degree of inanition produced. The most frequent result is a reduction of chloride with or without a reduction of base. The bicarbonate level is irregular.

Vomiting of HCl is not essential for this picture as it was encountered with esophageal obstruction in the absence of vomiting.

In a series of infections bicarbonate was generally about normal. In pneumonia it is usually normal while chloride is almost invariably low.

Anemia and polycythemia have no characteristic influence on the acids or base of the serum.

In diabetes (Peters, J. P., Bulger, H. A., Eisenman, A. J., and Lee, C.: VI, Studies of Diabetes. Jour. Clin. Invest., December, 1925, ii, No. 2, 167). Ketosis of considerable severity may develop without appreciably affecting the bicarbonate of the plasma. In these cases chloride is usually reduced and the base required for the neutralization of the organic acid is evidently derived from the chloride.

In severe diabetic acidosis the base required for neutralization of ketone acids is ceded by both bicarbonate and chloride. Chloride reduction may occur very rapidly and without augmented chloride excretion, indicating that the chloride ion is merely transferred to the tissues. In profound diabetic toxemia the salt content of the blood and probably of the tissues is seriously depleted. The bearing of these phenomena on the treatment of diabetic toxemia, ketosis, and acidosis is discussed in this paper.

In nephritis (Bulger, H. A., Peters, J. P., Eisenman, A. J., and Lee, C.: VII, Factors Causing Acidosis in Chronic Nephritis. Jour. Clin. Invest., February, 1926, ii, No. 3, 213), it appears that a reduction of total base and an increase of undetermined acids are the most significant factors causing acidosis in chronic interstitial and arteriosclerotic nephritis phosphates being less important. The degree of acidosis seems greatly influenced by variations of plasma chloride. With high chloride bicarbonate may be extremely low.

Beeson, B. B., and Church, J. G.: Superficial Yeast Infections of the Skin and of Its Appendages. Arch. Dermat. and Syph., May, 1926, xiii, 644.

The authors review the literature of yeast infections of the skin, call attention to the increasing number of cases reported, and report their study of a case of interdigital infection.

Cases with a geographic, well-marked border along with a loosened fringe of epidermis should be studied with yeasts in mind.

Many cases called "intertrigo" may be due to yeasts. Yeast infections seem capable of producing a variety of skin lesions and in lesions identical from a clinical standpoint different yeasts may be found.

McLean, A. B., and Sullivan, R. C.: Blood Sugar in Status Thymicolymphaticus: A New Theory as to the Cause of Sudden Death. Am. Jour. Med. Sc., May, 1926, clxxi, No. 5, 659.

The clinical picture in cases of status death being somewhat similar to that seen in "insulin shock," blood sugar determinations were made and a marked hypoglycemia found. In three cases the blood-sugar values were 42, 52 and 57 mg. per 100 c.c. In one case of suprarenal hemorrhage 25 mg. were found. In six cases of convulsions produced by conditions other than status thymicolymphaticus, and in six cases where determinations were made within one-half hour of death, normal values were found.

Acute suprarenal insufficiency is suggested as the immediate cause of sudden death in status thymicolymphaticus.

Hager, B. H., and McGath, T. B.: Etiology of Incrusted Cystitis with Alkaline Cystitis. Jour. Am. Med. Assn., Oct. 31, 1925, lxxxv, 1352.

Cultures from the urine in this condition gave a constant growth of a bacillus having the general characteristics of the bacillus found in the nasal discharges from ozena (Salmonella fetida), but which possesses sufficient cultural differences to cause the authors to regard it as a distinct species to which they give the name Salmonella ammoniae. The organism is capable of breaking urea into ammonia and carbon dioxide in a very short time.

The organism was found consistently in seven cases and when injected into the blad-

ders of guinea pigs in whom a chemical cystitis had been induced, an alkaline incrustation was produced.

Hager, in a later paper (Hager, B. H.: A Contribution to the Etiology of Calcareous Pyelonephritis. Jour. Urol., February, 1926, xv, No. 2, 133) demonstrated that this organism can invade the kidney pelvis and, under favorable conditions, produce a calcareous pyelonephritis.

Greenwald, H. M., and Eliasberg, H.: The Pathogenesis of Death from Burns. Am. Jour. Med. Sc., May, 1926, clxxi, No. 5, 682.

In two cases which presented a marked hypoglycemia experiments on rabbits (10) demonstrated that the cause of death in these animals may be divided into two stages: *a.* Initial stage due to shock and accompanied by hyperglycemia due to hyperactivity of the suprarenals; *b.* Secondary stage, due to degenerative changes, particularly in the suprarenals. The administration of adrenalin is indicated only in the secondary stage of suprarenal exhaustion.

McQuarrie, I., and Shohl, A. T.: A Colorimetric Method for the Determination of the P_H of Cerebrospinal Fluid. Jour. Biol. Chem., December, 1925, lxvi, 2.

The authors devised an apparatus (made by the Empire Laboratory Supply Co., New York), on the principle of the Van Slyke apparatus whereby loss of CO_2, contact with air, and transfer are all avoided.

The apparatus is figured in the paper.

Method.—Measure into the apparatus as many tenths of c.c. of Hastings' indicator solution (0.0075 per cent phenol red) as of c.c. of spinal fluid which it is expected to use. Connect the upper capillary tube directly to the lumbar puncture needle by means of a rubber tube bearing a glass Luer adapter previously sterilized, observing sterile precautions the while. Allow the fluid to escape under its own pressure through the side of the three-way stopcock which has been turned so as not to be connected with the apparatus. When all air has been removed from the capillary tube, allow the spinal fluid to enter the apparatus by turning the stopcock and holding the bulb in such a position that its mercury level is at or very slightly below that in the sampling tube. The flow of spinal fluid is stopped when the desired amount has entered. Place a pinchcock at the lower end of the apparatus. Immerse in a water-bath at 38° for five minutes and compare with the bicolorimetric standards.

A comparison of the blood and spinal fluid shows that the two normally have the same P_H: 7.35 to 7.40 ± 0.02.

Shivers, C. H. deT.: Clinical Value of Bismuth in Treatment of Syphilis. Arch. Dermat. and Syph., October, 1924, x, 414.

The author concludes that:

1. Bismuth should not be substituted for arsenic in primary or secondary syphilis, except in patients resistant to arsenical treatment.

2. Bismuth is effective, clinically, in the treatment of all forms of tertiary syphilis.

3. In the treatment of neurosyphilis, bismuth in some cases has proved itself superior to arsenic.

4. Bismuth should be tried in all patients who do not tolerate the arsenicals.

5. Bismuth should be given with caution in all patients with faulty elimination.

6. The absorption of this drug should be carefully studied, and if possible, the number of treatments given should depend on the roentgenologic findings.

He reports three cases in which chills, headache, bleeding gums, and a sense of oppression in the chest were noted due to a cumulative toxic effect.

Taccone, G.: A Cerebrospinal Fluid Test. Pediatria, February, 1926, xxxiv, 131.

A five per cent solution of bichromate of potash is heated and filtered, and after cooling, a number of drops of trichloracetic acid equivalent to the number of cubic centimeters of the solution are added. The reagent thus prepared will keep indefinitely. Addition of

trichloracetic acid may also be made as occasion requires. For example, from three to four drops of the acid may be added at the time to the three to four c.c. of the solution of bichromate of potash which are necessary for each test. Into a test tube of one centimeter in diameter which contains from three to four c.c. of the reagent is introduced one-half of one c.c. of the cerebrospinal fluid which is intended for examination and which has previously been freed from blood. The cerebrospinal fluid should be added drop by drop to the walls of the tube by means of a fine pipette during gradual application of heat in such manner that the two fluids are superimposed but are not mixed.

A positive reaction is said to manifest itself primarily by the formation in the zone of contact of the two fluids of a ring which in the cerebrospinal fluid of sufferers from meningitis becomes immediately denser and thicker than that produced by normal or by meningoencephalic types of cerebrospinal fluid, in which the quantity of albumin is either normal or is only slightly increased (since density and height of the ring are in direct proportion to amount of albumin contained in the cerebrospinal fluid), and, secondarily, by persistence of a ring which appears more or less thick and dense in cases of acute meningitis, and weblike in encephalic and medullary forms with scattered meningeal lesions. A negative reaction is declared to reveal itself by a total disappearance of the ring.

In a number of cases in which the test was applied by the author the reaction invariably yielded a positive result in acute meningitis, while in other pathologic conditions of the central nervous system, in which the principal lesions involved the nervous tissue in particular, it demonstrated the altered composition of the cerebrospinal fluid.

Garrod, L. P.: On the Action of Certain Alleged Intestinal Antiseptics. Brit. Med. Jour., February 27, 1926, 367.

Method.—About half a gram of feces is placed in a large sterile tube of known weight and accurately weighed. Sufficient sterile water is added to give a convenient dilution, such as 1 in 50. Complete emulsification is carried out by forcing the fluid in and out of a long syringe with a wide-bore needle (this process will do in two minutes what will occupy a mechanical shaker half an hour). Decimal or other convenient dilutions are then made from the emulsion, and from each of the last two, three, or four dilutions 0.1 c.c. is sown on to large plates, previously dried thoroughly (at least 5 per cent of the water in the medium being evaporated by standing on a 55° C. oven), and spread until the fluid sown has been absorbed by the surface of the medium, leaving it dry. After incubation the colonies are counted, and the results expressed in millions of living organisms of each type per gram of feces.

Cultures made by this method yield uniformly spaced discrete colonies, and, apart from their value as affording quantitative results, are superior to those made by the ordinary method.

The syringe employed for emulsification and the 0.1 c.c. pipettes for sowing had to be specially made for the purpose.

That the numerical accuracy of the results can be relied on was shown by duplicating the process, consistent results being obtained.

Four preparations—Dmol, Kerol, Yatren, and Izol—described as intestinal antiseptics and given by mouth when examined by the procedure above, were without appreciable influence on the number of living aerobic organisms in the feces.

Gross, M.: A Method of Reading Microreactions Macroscopically. Klin. Wchn., Feb. 19, 1926, v, 342.

The following method was used in the performance of the Meinecke flocculation test:

After the reagents are mixed in a glass dish a loopful of the mixture is taken up in a platinum loop measuring 0.04 cm. in diameter and inserted in a cork. The cork is then placed in a test tube containing a small amount of wet cotton and may be incubated in a rack as desired.

In this perpendicular position most of the liquid collects in the lower third of the loop. Readings are made by holding the tube against a window and looking through the loop.

Ramiroy Corria, C. M.: Technic for Selective Staining of Entameba in Sections. Semana Med., Nov. 12, 1925, xxxii, 1244.

1. Frozen sections of material fixed in formol.

2. The sections are placed in a receptacle containing silver carbonate to which a few drops of pyridin have been added (approximately three drops for each c.c.). Cover with a watch-glass, leaving a bubble enclosed, and heat over an alcohol burner, without permitting the heat to exceed about fifty degrees. This is accomplished by holding the receptacle between the fingers and very carefully moving it about, until the sections assume a yellowish tint.

3. Place the sections in a small glass dish with water and mount them, then stain the background; or

4. Stir and strengthen, with heat, by a 1:500 solution of gold chloride. Fix in sodium hyposulphite five per cent wash, and then apply any desired complementary stain. Only the nuclei must be stained black or purple, and the same coloration for the amebas, whose characteristic nucleus is seen in its protoplasm charged with inclusions. Differentiation is thus not necessary, and many sections can be stained at the same time, adding to the advantages of this procedure.

Oser, B. L., and Karr, W. G.: The Correction of Folin-Wu Blood-Sugar Values. Jour. Biol. Chem., January, 1926, lxvii, No. 1, 319.

A table is presented in which the error due to the failure of the blue color to vary directly in intensity as the concentration is corrected, the corrected value for the blood-sugar reading being shown in column 5.

BLOOD-SUGAR DETERMINATIONS USING STANDARD 2 (2 C.C. = 0.4 MG.)

COLORIMETRIC READING		RATIO STANDARD / UNKNOWN (3)	BLOOD SUGAR	
STANDARD (UNKNOWN SET AT 10) (1)	UNKNOWN (STANDARD SET AT 20) (2)		OBSERVED (x2) (4)	ACTUAL (y2) (5)
mm.	mm.		mg. per 100 c.c.	mg. per 100 c.c.
7.5	26.7	0.75	150	157.3
8.0	25.0	0.80	160	165.8
8.5	23.5	0.85	170	174.4
9.0	22.2	0.90	180	182.9
9.5	21.1	0.95	190	191.5
10.0	20.0	1.00	200	200.0
10.5	19.1	1.05	210	208.6
11.0	18.2	1.10	220	217.1
11.5	17.4	1.15	230	225.7
12.0	16.7	1.20	240	234.2
12.5	16.0	1.25	250	242.8
13.0	15.4	1.30	260	251.3
13.5	14.8	1.35	270	259.9
14.0	14.3	1.40	280	268.4
14.5	13.8	1.45	290	277.0
15.0	13.3	1.50	300	285.5
15.5	12.9	1.55	310	294.1
16.0	12.5	1.60	320	203.6
16.5	12.1	1.65	330	311.2
17.0	11.8	1.70	340	319.7
17.5	11.4	1.75	350	328.3
18.0	11.1	1.80	360	336.8
18.5	10.8	1.85	370	345.4
19.0	10.5	1.90	380	353.9
19.5	10.3	1.95	390	362.5
20.0	10.0	2.00	400	371.0

Corley, R. C., and Denis, W.: The Determination of Calcium in Tissues, Feces, and Milk. Jour. Biol. Chem., December, 1925, lxvi, No. 2, 601.

Method for the Determination of Calcium in Tissues.—Ten gm. of finely ground tissue together with 50 c.c. of 0.1 N sodium hydroxide are placed in a large Pyrex test tube (25 x 200 mm.) graduated at 60 c.c. The tube is covered with tinfoil and autoclaved for two hours at a temperature of 180° C. by which treatment practically complete solution is effected. The solution is now rendered strongly acid by the addition of concentrated hydrochloric acid, diluted with distilled water to a volume of 60 c.c., allowed to stand for at least thirty minutes, then filtered by suction through a Gooch crucible provided with a mat of calcium-free asbestos fiber or filter paper. We sometimes centrifuge the liquid before attempting to filter, a procedure which while not essential greatly facilitates the latter operation.

At this stage the solution should be clear and absolutely free from suspended particles; the color, however, varies greatly from the light yellow given by muscle to the dark reddish brown noted when liver is used. An aliquot of the solution (usually 15 c.c. in the case of normal tissues) is measured into a 50 c.c. conical centrifuge tube, a half volume of 4 per cent ammonium oxalate solution is added, and the reaction is made alkaline to methyl red by the cautious addition of concentrated ammonium hydroxide. This precipitation should be made shortly after filtration, as if the filtrate is allowed to stand too long the color gradually deepens and the further procedure becomes more difficult. After standing for at least one hour the precipitate is centrifuged down, and the supernatent liquid is poured off as completely as possible without disturbing the precipitate.

This precipitate is now dissolved in 5 c.c. of approximately normal sulphuric acid and titrated at room temperature with 0.1 N potassium permanganate until pink, and after a period of five to ten minutes there are added 5 c.c. of a 4 per cent solution of ammonium oxalate. As soon as the solution is perfectly clear 5 c.c. of water are added, and the reaction is adjusted to the neutral point of methyl red by the cautious addition of concentrated ammonium hydroxide, using approximately normal hydrochloric acid for back titrations if the reaction has passed the neutral point.

After standing for one hour or longer if convenient the precipitate is centrifuged down, the supernatant liquid poured off as completely as possible, and the calcium oxalate washed with 30 to 35 c.c. of ice-cold water, centrifuged again, and after decantation of the wash water, the precipitate is dissolved in 5 c.c. of approximately normal sulphuric acid, the tube placed for five minutes in a water-bath at 70° C., and the solution then titrated with 0.1 N potassium permanganate.

The blank titration given by the sulphuric acid is subtracted. Since 1 c.c. of 0.01 N potassium permanganate is equivalent to 0.2 mg. of calcium, the calculation is as follows:

$$\text{mg. per 100 gm. sample} = \text{titration} \times \frac{0.2 \times 60}{\text{aliquot}} \times \frac{100}{\text{sample in gm.}}.$$

Using a 10 gm. sample of tissue and a 15 c.c. aliquot this equals the titration times 8.

Method for the Determination of Calcium in Milk and in Feces.—The autoclave method has been applied successfully to the determination of calcium in milk and in feces, although on account of the smaller amount of protein and other hydrolyzable organic matter present it was found necessary to modify the procedure somewhat.

One c.c. of cow's milk, 5 c.c. of human milk, or 1 gm. of feces, is introduced into a large test tube and autoclaved for one hour at 160° C. with 50 c.c. of 0.01 N sodium hydroxide solution. The remainder of the procedure is identical with that described for muscle.

Method for Determination of Calcium in Bone.—After the broken bone (in weight from 5 to 10 gm.) has been digested in the autoclave with 50 c.c. of tenth normal sodium hydroxide, the alkaline liquid is carefully poured off, and the remaining inorganic framework is dissolved by the addition of about 15 c.c. of concentrated hydrochloric acid. The acid and alkaline extracts are combined, diluted to a known volume, and the calcium determined in an aliquot by the procedure described for the other tissues.

Campbell, W. R.: Quantitative Determination of Dihydroxyacetone. Jour. Biol. Chem., January, 1926, lxvii, No. 1, 59.

Solutions.

Dihydroxyacetone.—A 1 per cent solution is prepared by dissolving 1 gm. of dihydroxyacetone, previously kept in a desiccator, over phosphorus pentoxide until no further loss of weight occurs, and making up to 100 c.c. with distilled water. A few drops of toluene or of xylene are added and well shaken. The solution keeps a week.

Dihydroxyacetone 0.01 per cent solution.—This solution containing 0.1 mg. per c.c. is made by diluting 1 c.c. of the foregoing solution to 100 c.c. with distilled water in a volumetric flask. For the preparation of solutions containing 0.05 mg. per c.c. and 0.2 mg. per c.c. a 200 c.c. and a 50 c.c. volumetric flask is used respectively. A few drops of toluene are added. The dilute solution should be made daily.

$KMnO_4$ solution, 0.2 N.—This is made up in the usual way, using 6.324 gm. of pure potassium permanganate per liter of distilled water, allowing to age for a few days, filtering, and titrating against a known quantity of 0.1 N sodium oxalate solution with 5 c.c. of concentrated H_2SO_4 in a volume of 150 c.c. at 70° C.

$KMnO_4$ solution, 0.01 N.—This solution is made fresh daily by diluting 0.2 N $KMnO_4$ solution to twenty times its original volume. Its titer should be carefully checked by test against an 0.01 N sodium oxalate solution, freshly diluted from 0.1 N sodium oxalate solution, to which 1 c.c. of 50 per cent H_2SO_4 has been added, and the solution kept at 70° C. during titration.

Sodium Oxalate Solution, 0.1 N.—The solution is made from United States Bureau of Standards sodium oxalate recently dried at 110° C. for three hours and kept in a desiccator. Six and seven-tenths gm. of the pure dry salt are weighed out, dissolved, and made up to a liter with water. The addition of 5 c.c. of concentrated H_2SO_4 facilitates solution.

Sodium Oxalate Solution, 0.01 N.—This is made by accurate tenfold dilution of the preceding solution of 0.1 N sodium oxalate.

Phosphate Molybdate Solution.—To a liter beaker containing 35 gm. molybdic acid and 5 gm. sodium tungstate add 200 c.c. of 10 per cent sodium hydroxide and 200 c.c. of water. Boil vigorously twenty to forty minutes to expel ammonia, and cool. Dilute to about 350 c.c., add 125 c.c. of concentrated (85 per cent) phosphoric acid, and dilute to 500 c.c.

Colorimetric Method.—After suitable dilution of the fluid containing dihydroxyacetone 2 c.c. of the diluted solution are mixed with 2 c.c. of the phosphate molybdate solution in a Folin-Wu blood-sugar tube and boiled in a water-bath for fifteen minutes. The tube is then cooled in running water. The contents of the tube are diluted to 25 c.c. and compared in a colorimeter with the color developed from a suitable standard solution of dihydroxyacetone similarly treated. Standard solutions containing 0.5, 0.1, and 0.2 mg. of dihydroxyacetone per c.c. furnish suitable standard colors. Standard solutions of glucose are not quite satisfactory owing to a slight difference in the quality of the colors.

Comment.—The unknown should not be less than three-fourths, nor more than one and one-half times the strength of the standard, as the colors do not exactly match if these limits are exceeded.

When blood is being examined the tungstic acid filtrated as prepared by Folin and Wu is used. To 2 c.c. of oxalated blood 14 c.c. of water, 2 c.c., of 10 per cent sodium tungstate, and 2 c.c. of $\frac{2}{3}$ normal H_2SO_4 are added in the order given, mixing after each addition, and well shaken and filtered after standing ten minutes. The filtrate is used undiluted in the method as described above, and a correction applied for the glucose and other reducing substances in the filtrate. When a standard set at 20 mm. is used, the amount of the unknown is read off on the graph and 0.05 mg. is subtracted. This purely empirical correction allows for glucose and other reducing substances in the filtrate.

Volumetric Method.—Two c.c. of the suitably diluted solution are boiled fifteen minutes with an equal quantity of the acid phosphate molybdate solution and then cooled. The further procedure consists in reoxidizing the undiluted blue solution in the cold with 0.01 N

$KMnO_4$ solution from a recalibrated burette graduated in $\frac{1}{50}$ c.c. One and fourteen hundredths c.c. of 0.01 N $KMnO_4$ equal $\frac{1}{5}$ mg. of dihydroxyacetone itself; or, using a Folin-Wu blood filtrate, 1.14 c.c. of the permanganate solution equal 1 mg. of dihydroxyacetone per c.c. of original blood.

In carrying out this titration the permanganate solution is added slowly drop by drop, with shaking, to the cold blue solution until all blue color just disappears, leaving a colorless water-clear solution. Titrating to the first pink tinge is unnecessary as the disappearance of the blue color furnishes a satisfactory end-point. When the quantities of dihydroxyacetone are large, 1 c.c. of 4 N H_2SO_4 may be added to dissolve the oxide of manganese formed.

Scott, W. J., and Leonard, V.: Hexylresorcinol in the Treatment of Pyelitis of Infancy and of Childhood. Am. Jour. Dis. Child., February, 1926, xxxi, 241.

Report of a clinical study. The drug was administered as a 2.5 per cent solution, a teaspoonful (0.1 gm.) t. i. d., the dose being gradually increased to 0.2 or 0.3 gm. t. i. d.

No toxic effects were noted. Occasional intolerance, evidenced by cramps and diarrhea disappearing upon decrease or withdrawal of the drug. The dose may be continued indefinitely.

On the basis of clinical experience with hexylresorcinol in the treatment of pyelitis in children, it is believed that it is at times a distinct addition to the therapeutic measures heretofore avoided.

The striking improvement in the general health and nutrition, frequently observed in children taking hexylresorcinol, does not seem to be entirely dependent on the control of the urinary infection, for it may occur long before there is any noticeable improvement in the local condition and is sometimes the most impressive effect of the treatment.

To obtain the best results, treatment should be persistent, the fluid intake should not be increased, and so should be avoided during administration of the drug.

Leonard, V., and Frobisher, M.: Clinical Application of Hexylresorcinol in Urology with Observations on the Significance of Surface Tension in Urinary Antisepsis. Jour. Urol., January, 1926, xv, 1.

The successful application of hexylresorcinol in the treatment of chronic infections of the urinary tract depends therefore upon the strict observance of four factors; all of which bear a distinct relationship to the surface tension of the urine.

1. The dosage must be adequate (0.6 grams three times daily). On smaller doses there may be insufficent reduction of the surface tension of the urine.

2. The fluid intake must not be increased for this not only dilutes the active hexylresorcinol in the urine but renders even that dilution less effective than it would be otherwise, by raising the surface tension.

3. Sodium bicarbonate must be avoided for this drug raises the surface tension of the urine so markedly as to rob it of its bactericidal properties.

4. The course of treatment should be uninterrupted and sufficiently prolonged. The organisms which are most resistant to surface tension changes in the test tube (B. coli group) are most resistant to the action of hexylresorcinol in the urinary tract. Chronic B. coli infections ordinarily require from sixty to ninety days continuous treatment on doses of 0.6 gram (4 capsules) three times daily. Chronic coccus infections, on the other hand, may clear up completely with startling rapidity (forty-eight hours) and ordinarily require less than three weeks treatment.

Elvehjem, C. A., and Hart, E. B.: Quantitative Methods for the Determination of Iron in Biologic Materials. Jour. Biol. Chem., January, 1926, lxvii, No. 1, 43.

Standard Iron Solution.—Dissolve 0.7 gm. of ferrous ammonium sulphate (dried to constant weight) in 100 c.c. of distilled water and add 5 c.c. of concentrated sulphuric acid. Warm the solution slightly and add potassium permanganate until the iron is completely oxidized. Dilute the solution to 1 liter. One c.c. of the standard iron solution equals 0.1 mg. Fe.

A 10 per cent solution of potassium thiocyanate.

N/5 Potassium Permanganate.—Dissolve 6.30 gm. of the salt in distilled water and dilute to 1 liter.

Hydrochloric Acid.—Concentrated, free from iron.

Nitric Acid.—Concentrated, free from iron.

Molybdate Solution.—A solution of ammonium molybdate prepared in the usual manner on which a blank iron determination has been made to insure its freedom from iron.

Forty per cent Solution of KOH.—Prepared to be iron-free by making a 40 per cent solution and allowing to stand for several days, decanting the iron-free solution from the top.

Procedure.—A sample of the material to be analyzed is weighed out so as to contain between 0.1 to 0.3 mg. of Fe. In the case of liquid milk 50 c.c. are used and evaporated to dryness. The sample is then carefully ignited in an electric furnace. A platinum dish is preferable for the ignition although a previously ignited and acid-washed porcelain evaporating dish may be used successfully. The ash is taken up in about 10 c.c. of H_2O and 5 c.c. of concentrated HCl and allowed to stand for several hours. The residue is filtered off and the phosphorus removed from the filtrate in the usual manner, which consists of adding concentrated NH_4OH until the solution becomes cloudy, clearing up with concentrated HNO_3 in excess. Thirty c.c. of ammonium molybdate solution is added, digested on a water-bath at 65° C. for one-half hour, and the yellow precipitate of ammonium phosphomolybdate filtered off. The precipitate is carefully washed with dilute HNO_3 (9 c.c. HNO_3 in 100 c.c. H_2O) to insure the removal of the last traces of iron to the filtrate. Redigestion is not necessary as the small traces of phosphorus remaining in the filtrate will not interfere. The solution is brought almost to a boil and 40 per cent KOH (iron-free) is added until no further precipitate forms; usually about 20 c.c. are required. The solution is boiled for several minutes to remove the ammonia present. The solution is allowed to cool and if the hydroxides do not settle properly a few c.c. of KOH are added and heated further. The precipitate is filtered off on an asbestos Gooch crucible, which has been carefully washed with HCl, by decanting with clear liquid first and finally adding the precipitate to the Gooch crucible. The precipitate is washed with very dilute KOH solution (1 to 2 per cent). Best results are obtained if only a low pressure is maintained on the suction flask during filtering. The precipitate is dissolved from the Gooch crucible with 2.5 c.c. of concentrated HCl, which is added in several portions (a few drops at a time) washing with water after each addition of acid. In this way the iron may be dissolved off completely and the total filtrate kept below 30 to 35 c.c. The best method handling this small amount of solution is to introduce a test tube into the suction flask, allowing the end of the funnel to reach into the test tube so that the solution will be caught in the test tube instead of the suction flask. The solution in the test tube is then washed into the original beaker and the iron determined colorimetrically by adding enough N/5 $KMnO_4$ to produce a faint pinkish color (usually 1 to 2 drops) then adding 5 c.c. of a 10 per cent solution of potassium thiocyanate and making up to 50 c.c. volume in a volumetric flask. The color produced is compared in a Duboscq colorimeter with a standard color developed by taking 1 c.c. of the standard iron solution, adding 1 to 2 drops of N/5 $KMnO_4$ and 5 c.c. of the 10 per cent solution of potassium thiocyanate, and making up to 50 c.c. volume. The standard solution is set at 20 in the Duboscq and the unknown adjusted until the colors are equal. Since the standard contains 0.1 mg. of iron, the amount of iron in the unknown is readily calculated. If the variation in the readings of the standard and unknown is too great a smaller or larger amount of the standard should be taken as the case may be.

Under certain conditions some difficulty may be experienced in filtering the precipitate of the hydroxide on the asbestos Gooch. This may be remedied by adding a small amount of ammonium oxalate (20 c.c. of 2.5 per cent solution) to the solution before addition of the KOH. Due to the presence of the oxalate the calcium will be precipitated as the oxalate, making the precipitate more crystalline and easier to filter. Of course, in this case, after filtering, the Gooch crucible must be dried and held in a flame for a short time to remove the oxalate or it will interfere with the color development. Upon ignition the cal-

cium oxalate is changed to $CaCO_3$, and if care is taken not to continue the heating long enough to form CaO it is easily dissolved in the amount of HCl we have suggested. We do not believe this scheme necessary as we have experienced no great difficulty in filtering in any of the determinations we have made. However, we have used this departure with success and it may be found to be useful in some cases.

Birkhaug, K. E.: Observations on the Etiology and Treatment with Erysipelas Antistreptococcic Serum. Jour. Am. Med. Assn., May 8, 1926, lxxxvi, 1411.

Evidence is accumulating that erysipelas is due to a specific strain of the Streptococcus hemolyticus. Clinical trials in sixty moderately severe cases of erysipelas have demonstrated that intramuscular injection of erysipelas antistreptococcic serum, in amounts of 100 c.c. of unconcentrated, or 15 to 20 c.c. of concentrated serum, when administered during the first three days of the disease, causes a prompt lessening of the toxic depression, a critical fall in the temperature and pulse rate, prompt fading of the lesions, and rapid absorption of the blebs and edema in the affected areas. In late cases the effect is strikingly favorable though repeated injections may be necessary. By means of a skin test dose of toxin injected intradermally and simultaneously with the intramuscular therapeutic dose, it is possible to observe whether complete neutralization of the circulating toxins is accomplished or whether an inadequate dose of serum was administered. It cannot be stated as yet whether the serum is purely antitoxic.

Neuhof, H., and Cohen, I.: Abdominal Puncture in the Diagnosis of Acute Intraperitoneal Disease. Annals Surg., April, 1926, 454.

Exploratory abdominal puncture, in the opinion of the authors, is a valuable diagnostic aid in obscure acute abdominal disease and should be employed in every obscure intraperitoneal lesion for which operation may be indicated.

The abdominal wall is prepared as usual and the skin either frozen or anesthetized with novocaine. A lumbar puncture needle to which a 10 or 20 c.c. syringe is accurately fitted is employed and a puncture made through the rectus muscle or near its outer border. The site of puncture can often be placed in the line of a probable laparotomy incision. To avoid carrying in bits of skin and to preserve delicacy of touch when the needle is introduced a small skin incision is made before the puncture. Aspiration is not employed over the site of a palpable or questionable mass nor in any acute or chronic intraabdominal disease in which a loop of intestine may be fixed.

The needle with stylet in place is introduced perpendicularly with a slow even pressure. When the peritoneal cavity is entered the syringe is attached and gentle suction maintained for several seconds and while the needle is being withdrawn. The fluid withdrawn, of which there may be only a drop in the lumen of the needle, may be examined in various ways and may furnish valuable information of diagnostic importance.

Duggan, W. E., and Scott, E. L.: A Critical Examination or Four Methods Commonly Used for the Determination of Sugar in the Blood. Jour. Biol. Chem., January, 1926, lxvii, No. 1, 287.

The Folin-Wu and Hagedorn methods were found to be accurate and fairly precise when used to determine the concentrations of pure glucose solutions approximating those encountered in blood analysis.

It was found that an increase in the concentration of either the sugar or of the picric acid in the Benedict method would lead to high results, and this is offered as at least a partial explanation of the high results obtained by this method in certain pathologic bloods.

The Shaffer-Hartmann method was found to be reliable and satisfactory for concentrations above about 25 mg. per 100 c.c. of blood. Certain corrections also appear to be necessary to their table. A substitute table is submitted.

Lash, A. F.: A Comparison of the Incidence of Skin Reactions of the Toxins from Hemolytic Streptococci from Puerperal and Scarlet Fever. Jour. Am. Med. Assn., May 8, 1926, lxxxvi, 1427.

A study was made of 247 women, 20 nonpregnant normal, 86 normal pregnant, 141 normal puerperal.

The Streptococcus hemolyticus from puerperal fever is not one of the scarlet fever strains.

A low incidence of positive reactions both to the Dick and puerperal toxins was encountered, probably due to inherent immunity. The reaction to the two toxins in the same patient indicates that a person may be immune to one strain and not to another.

Kulp, W. L.: A Method for the Staining of Bacterial Flagella. Stain Technology, April, 1926, i, No. 2, 60.

A method is described with which nearly 100 per cent success has been obtained with nearly all species of bacteria.

Reagents.

Mordant Solution.—

20 per cent solution of tannic acid ..... 50 c.c.
(made by moistening 20 grams, transferring to a 100 c.c. flask and making up to volume with distilled water)
Cold, saturated solution of ferrous sulphate in distilled water 25 c.c.
Saturated 95 per cent alcoholic solution of basic fuchsin, Coleman and Bell ..... 5 c.c.

Mix and allow to stand eighteen to twenty-four hours. The precipitate is removed by filtration through asbestos or by centrifuging. The solution is then allowed to stand over night in a Coplin jar and used without further filtering or centrifuging.

Staining Solution.—

Freshly filtered saturated solution of anilin water ..... 100 c.c.
Saturated 95 per cent alcoholic solution of basic fuchsin ..... 12 c.c.

Mix and allow to stand eighteen to twenty-four hours, filter or centrifuge and transfer to Coplin staining jar.

Preparation of Culture.—A fresh agar slant having an appreciable amount of condensation water at its base is inoculated with the test organism and incubated at optimum temperature for twenty-four hours. At the end of this time a new slant is inoculated from the condensation water. After twenty-four hours' incubation of the second culture one or two drops of the condensation water (showing heavy growth) are poured aseptically into a large tube of sterile distilled water. Tubes having a diameter of one inch and containing 15 to 20 c.c. distilled water offer a particular advantage here. These water cultures are incubated at optimum temperature for from forty-eight to seventy-two hours. As a rule, seventy-two hours are preferable to shorter periods.

After this incubation period a loopful of the water culture is transferred carefully to a clean glass slide. The loop is filled by dipping into the culture without stirring or shaking, and transferred to the slide by touching the latter without drawing the loop over the surface or disturbing the suspension more than is necessary, as flagella are broken off easily in this stage of the procedure. The drop on the slide is allowed to dry at room temperature or in a 37° C. incubator. No flame or heat higher than 37° C. is employed for drying.

Staining Method.—1. Place the slide in the mordant solution for fifteen minutes at room temperature (20°-23° C.). 2. Wash carefully in a slow stream of running water and shake off the excess water. 3. Place in staining solution at room temperature for fifteen minutes. 4. Wash as in 2. The precipitate on the under surface may be wiped off. 5. Dry and examine.

The method, *exactly followed*, has given excellent results with organisms of the colon-typhoid group and several others.

Kornhauser, S. I.: A Quick Iron-Hematoxylin Method (as applied to fecal smears). Stain Technology, April, 1926, i, No. 2, 78.

A small part of the feces was rubbed up on a clean slide in physiologic salt solution and examined under the microscope for active protozoa. Then a drop of Donaldson's iodine-eosin stain was added to bring out the cysts. This concluded the preliminary examination, and if the case were positive, four permanent slides had to be made for confirmation and as a matter of record. Four clean slides were taken and numbered with a diamond to correspond to the patient's number in our daily record. A clean applicator stick was then used to obtain material which contained mucus or blood, if such was present, and streaked lightly on the slide. The slides were then dipped without drying into Coplin jars of hot Schaudinn's fluid, left there five minutes, washed in 50 per cent alcohol, then 50 per cent alcohol plus iodine to remove any bichloride, 35 per cent alcohol, then water. The wet slides were then placed on an electric hot plate and a 4 per cent iron alum solution was dropped on until the slides were covered and steaming. Any evaporation was taken care of by the further addition of iron alum from a pipette. This was continued for several minutes. Slides were then rinsed in water, put back on the hot plate and a ripe 0.5 per cent hematoxylin solution was added by means of a pipette, the slide being kept full of liquid and steaming all the while. After several minutes, they were placed in water, differentiated in cold 2 per cent iron alum solution, controlling the decolorization from time to time under the microscope. When the nuclei in the best parts of the smear stood out nicely, decolorization was stopped and the slides washed in running water for at least five minutes. They were then dehydrated and mounted in balsam in the usual manner.

Thus within a half hour it was possible to have finished permanent slides with fine cytologic details shown to their best advantage. These preparations are now about seven years old and they are still as good as they were originally.

It might be added that experience with hematoxylin shows that black crystals would not do for this work, but that the white or light brown crystals made up in 10 per cent solution in alcohol and ripened and then added to water to make up 0.5 per cent hematoxylin would work nicely.

Burke, V., and Ashenfelter, M.: Notes on the Gram Stain. Stain Technology, April, 1926, i, No. 2, 63.

1. The P_H of the environment in which organisms are grown may affect the Gram reaction.

2. Organisms should be classed as Gram-positive or Gram-negative according to the staining reaction when grown in the optimum P_H range for the species. Since the reaction may change with growth the media should be strongly buffered.

3. An alkali should be incorporated in the Gram staining technic in order to nullify the effect of an acid environment. We frequently wish to stain organisms from an environment not subject to control.

4. If alkali is added to the staining technic and the best American dyes are used the reaction of the medium upon which organisms are grown should not affect the Gram reaction.

5. There is no relation between acid and alkali production and the classification of bacteria regarding the Gram reaction. Acid and alkali producers are found in both groups.

6. The selection of a Gram staining technic should be based upon reliability of the methods under unfavorable conditions of acidity as well as on results obtained with borderline organisms.

There is included a discussion of the requirements of a practical Gram stain.

Hach, T. W.: Cultivation of the Gonococcus and Meningococcus. Münch. med. Wchn., Feb. 12, 1926, lxxiii, 275.

Hach is enthusiastic over the efficiency of Hibler's medium prepared as follows:

Clean the brain from skins and mince it in the mincing machine. Strain it through gauze. Add an equal quantity of physiologic salt solution (85 per cent), stir well and fill

test tubes of 5 to 7 c.c. with the substance. Sterilize for twenty minutes in the autoclave under 2 atmospheres pressure. Over the 5 to 6 cm. of a more or less homogenic sediment will be seen 1 cm. of a liquid which is not always quite clear. The reaction of this medium is acid; P_H 6.2 to 6.5.

Miller, J. W.: The Weigert-Pal Technic for Staining Myelin. Stain Technology, April, 1926, i, No. 2, 72.

A method is described by which three difficulties of the original technic are overcome: the tendency of the sections to become brittle, the difficulty of observing the reaction in the permanganate solution; and the slowness of the reaction.

1. Formalin fixed material is embedded in celloidin and sections 75 to 90 microns are cut. Sections of this thickness show the fiber tracts very well.

2. Mordant in Müller's fluid in a warm place, for twelve to eighteen hours. A paraffin oven at 35 to 39° C. is best.

3. Wash several times in distilled water.

4. Stain eight to twenty-four hours in Weigert-Pal hematoxylin made as follows: 10 c.c. of 10 per cent ripe hematoxylin solution in absolute alcohol. 90 c.c. of distilled water. 1 c.c. of 1 part saturated solution of lithium carbonate to 80 parts of distilled water.

5. Wash in distilled water with a few drops (6 to 8 to 1000 c.c. water) of lithium carbonate for three to five minutes.

6. Place sections in 50 per cent alcohol for a few minutes.

7. Then in 80 per cent alcohol for ten to twelve hours. This step makes the sections less brittle and the differentiation easier.

8. Pass back through 50 per cent alcohol to water.

In the following steps of differentiation two large Petri dishes containing the permanganate and oxalic acid solutions and a large crystallization dish containing distilled water are placed on the improvised glass hot plate, which illuminates the potassium permanganate solution and warms both the permanganate and oxalic acid solutions.

9. Place sections in a 0.25 per cent aqueous solution of potassium permanganate until brown (one-half to three minutes). The gray matter can be seen through the illuminated solution as a light brown.

10. Rinse in distilled water one to three minutes.

11. Place in a freshly prepared solution of equal parts of a 1 per cent aqueous solution of oxalic acid and a 1 per cent aqueous solution of potassium sulphite, to remove the brown color. This should leave the myelin a dark blue to black color and the gray matter a pale gray or white. If all the brown color does not come out, repeat the treatment with permanganate solution a short time. The potassium sulphite must be fresh for good results.

12. Wash in 3 changes of distilled water.

13. Dehydrate through 50 per cent, 80 per cent and 95 per cent alcohols.

14. Clear in origanum oil or better carbol xylol.

15. Mount in neutral balsam.

By this method as many as 300 sections may be stained and differentiated in the time it usually took to handle 50.

REVIEWS

Books for Review should be sent to Dr. Warren T. Vaughan, Medical Arts Building, Richmond, Va.

*Neurological Fragments**

THE passing of a truly great man without contemporary biographical discussion or better—autobiographical contributions, constitutes a permanent loss to posterity. Opinion differs as to whether biography or autobiography is of greater value, but the greatest source of pleasure in the study of a man's life and activity comes from a reading of both and a comparison of those viewpoints expressed within.

Dr. Jackson, known to all neurologists and best known to the medical profession in general as the first to describe what is now known as Jacksonian epilepsy, left no memoirs, and yet his life was one full of interest and his opinions served to direct in great degree subsequent neurologic progress. Dr. Taylor has collected many of his scientific contributions, those originally published by Dr. Jackson over a long period of years under the group title *Neurological Fragments*, and has published them with three biographical sketches. This combination of biography and the written word by which we may trace the writer's mental development, constitute a fair substitute for a true autobiography.

An Introduction to the Study of X-Ray and Radium†

THE volume is based upon a series of demonstrations given at King's College Hospital and presents those facts concerning x-rays and radium which will afford the reader an idea of their nature and application. The technic of clinical examination and the interpretation of findings are not included. The book covers the knowledge in pure and applied physics relating to radiology which must of necessity form the groundwork of a comprehensive understanding of roentgenology. We find chapters on radioactivity, the preparation of radium salt, the preparation and measurement of radium emanation, the action of radium upon normal living tissues, the atomic theory, methods of protection against the x-ray and radium, and notes on x-ray and radium therapy. The historical description of the development of clinical radiology is of particular interest.

It is with some interest that we note that the authors do not recommend x-ray treatment as a sole procedure in operative malignancy. They feel that where there is a possibility of cure from surgical extirpation, this should be done. Of course x-ray therapy is used in conjunction with surgery.

The volume should be recommended to all radiologists, to undergraduate students at the beginning of their acquaintanceship with roentgenology and to those practitioners who are referring their work to the roentgenologist and wish to have a first hand acquaintance with what is actually being done.

*Neurological Fragments. By J. Hughlings Jackson, M.D., F.R.S., F.R.C.P., with biographical memoir by James Taylor, M.D., F.R.C.P., and including the "Recollections" of the late Sir Jonathan Hutchinson and the late Dr. Charles Mercier. Cloth. Oxford Univ. Press, 1925.

†An Introduction to the Study of X-rays and Radium. By Hector A. Colwell, M.B. (Lond.) D.P.H. (Oxf.) and Cecil P. G. Wakeley, F.R.C.S. (Eng.) F.R.S. (Edin.) Cloth Price $3.35. Pp. 203. Illustrated. Oxford Univ. Press. 1926.

NOTE: Insofar as practicable the book review section will present to the reader (a) interesting knowledge on the subject under discussion, culled from the volume reviewed, and (b) description of the contents so that the reader may judge as to his personal need for the volume.

We trust that the scientific information printed in these pages will make the reading thereof desirable per se and will thereby justify the space allotted thereto.

*Bacteriology and Applied Immunology for Nurses**

BEGINNING with a brief history of the science of bacteriology the author proceeds with a description of bacteria in general and their classification, methods of cultivation, examination and staining, and methods for their destruction.

After pointing out that most bacteria are not disease producers, he outlines briefly the mode of production of disease by bacterial infection, describes the bacteriologic characteristics of the more important bacteria and proceeds with discussion of the mechanism of infection. This carries us naturally to the subject of immunity and the mechanism of its production. The author selects Ehrlich's side-chain theory as suitable for presentation and the most easily visualized and comprehended. At the same time he wisely italicizes the remark that the illustrative figures have no actual counterpart in the cells of the body and are purely imaginary.

An understanding of the general principles of immunity having been acquired, the work now proceeds with discussion of their practical application in applied immunology. The nurse becomes acquainted briefly with the agglutination test in typhoid, dysentery, pneumonia, and in blood grouping; with the luetin test, the tuberculin test, the Schick test, the pollen reactions and the complement-fixation test. Following these procedures which are of value in diagnosis there is a section devoted to immunologic methods of treatment including the preparation and use of serums and a discussion of the phenomenon and treatment of anaphylaxis.

We find chapters on the bacteriology of milk, water, and foodstuffs, the collection of specimens for laboratory examinations, a most important chapter too often not understood by the present-day nurse, chapters on protozoa, etc.

The introduction is excellent. It stresses the knowledge that the function of the nurse is to assist nature. The author points out that because of her intimate relationship with the patient and the public, her part in the education of the people at large can be and must be of great importance. She should be well prepared to give an intelligent reason for the use of vaccines and serums and know what they are and how they act, what they will and will not do, how vaccination will serve as a preventive against smallpox and typhoid fever and how to answer and confute objections to the use of these methods. "The ability to do this represents the difference between a fully trained and equipped nurse—a real guardian of the public health—and a mere attendant, trained more or less in the mechanical duties of the sick room."

After having read the introduction one wishes that it might be reproduced in toto at the end of volume for it is after having become acquainted with the science of bacteriology and immunology that the nurse can first truly appreciate the remarks of the introduction. However, the author has improved on this idea for the closing chapters of the volume deals with the prevention of disease, the immunization of the individual, applied sanitation, vivisection and the education of the public.

The illustrations are excellently done and the physical craftsmanship of the volume is unusually good.

Midwifery Mechanics†

THIS is not simply a text on the mechanical principles involved in the successful delivery of a living child in the various presentations, but is a monograph on the author's conception of the fundamental mechanical principles of parturition.

Since the time of Hippocrates obstetricians have sought out ways and means of lightening the labor of a parturient mother. So much so that nowadays whenever a novel suggestion is put forth, such as twilight sleep or a recently popularized form of version, our first reaction is of an adverse nature and our first question is as to the ultimate result, particularly the maternal or infant mortality.

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*Bacteriology and Applied Immunology for Nurses. By Robert A. Kilduffe, A.B., A.M., M.D. Director Laboratories, Atlantic City Hospital. City Bacteriologist, Atlantic City, N. J. Consulting Serologist, Providence Hospital, Beaver Falls, Penna. Major Medical Corps. Altho Leather. Illustrated. Price $2.00. Pp. 252. The Bruce Publishing Company. Milwaukee, 1926.

†Midwifery Mechanics. By Lieut.-Colonel Andrew Buchanan, I.M.S. (Retd.), M.A., M.D., M.Ch., M.A.O. Cloth. Price $2.50. Pp. 82. Illustrated. Oxford Univ. Press. First printed 1924.

Dr. Buchanan, however, offers no startlingly new methods designed to improve on those already found so successful by nature.

His first and foremost objective is to explain the mechanism of normal delivery in terms that will be more readily understood by the students of obstetrics. His explanation is certainly original and is readily understood, particularly so since the monograph is abundantly and excellently illustrated with diagrammatic sketches and with photographs of his illustrative mannikins. The principle on which the entire discussion is based is the need for juxtaposition of two pivot points, one in the female pelvis and one in the fetus. When these two points are close together delivery becomes a simple matter, when they are widely separated, trouble ensues. The space available in this review does not permit a more detailed exposition of this theory of pivot points.

Where the pivot points are widely separated so as to interfere with satisfactory rotation of the head through the pelvis around the pubic symphysis as an axis, the author describes the methods best calculated to procure closer approximation.

The volume should appeal to curious minded obstetricians rather than to obstetric faddists.

*Pulmonary Arteritis**

THE volume, written in Spanish, presents in an interesting fashion an original study of sclerosis of the pulmonary artery.

The purpose of the volume has been adequately set forth. The author with some of his coworkers, maintains that sclerosis of the pulmonary artery exists as a primary affectation in which syphilis plays the most important rôle as a causative agent and that the disease also exists as a clinical entity capable of being diagnosed.

The earliest symptoms are cyanosis and dyspnoea. *Cyanosis* manifests itself first, being marked and localizing itself principally in the face. The extremities however are also strikingly affected. It is this striking cyanosis that led Ayerza to name the disease "Cardiacos negroes."

Dyspnea follows months, at times years, later. The interesting thing about this symptom is that it may go on indefinitely in the absence of the other mechanical concomitants, that is, edema, hepatic congestion, congestion of the lungs, etc. These however with cardiac insufficiency appear later and may last several years.

A little hemoptysis presents itself with a certain regularity in these patients.

Headaches are of frequent occurrence, having no exact localization. They are very constant and mostly nocturnal.

Faintness and giddiness coming in spells are symptoms.

Finally, a strange symptom that appears in the late stages of the diseases is hypersomnia.

The author has surveyed and reviewed the material and literature on the subject systematically and with thoroughness. His investigations are clearly presented, and the anatomic, histologic and pathologic studies that he includes help the reader to obtain a more comprehensive picture of the lesion found in this disease.

It is interesting to note that the so called "black cardiac cases" are synonymously known by many names, and because the author believes that the arterial process involved is an inflammatory reaction, he has purposely chosen the title *La Arteritis Pulmonar* for his volume.

Though the author maintains that pulmonary arteritis exists as a primary disease and that certain cardiac diseases and chronic pulmonary diseases are only factors of a secondary nature, the reviewer feels that where syphilis is not definitely found the evidence is not entirely satisfactory that it is a primary disease and that here cardiac and chronic pulmonary diseases play more than a secondary rôle in its etiology.

It is an admirable piece of work, one giving the clinician or diagnostician valuable information, and since the author has put down a definite line of symptoms for its manifestation, it should be of importance in the field of differential diagnosis.

*La Arteritis Pulmonar y su cuadro clinico por F. C. Arrillaga. Pp. 274. Paper, Buenos Aires. "El Ateneo" Libeeria cientifica y literaria de Pedro Garcia.

*The Diagnosis, Treatment and End-Results of Tuberculous Disease of the Hip Joint**

THE author sets forth his thesis so clearly in his introduction that we quote him at some length.

"In discussing diagnosis attention has been focussed on the diagnosis of the early case. Our aim should be the recognition of the presence of tuberculous disease at the earliest possible moment. Consequently, no mention is made of the former customary division of the disease into three stages; only the signs and symptoms of early disease are commented upon.

"The treatment meted out for tuberculous disease of the hip joint has varied from decade to decade. Amputation, which was at one time the sole resort of the surgeon, was superseded by the operation of excision of the head of the femur. When the poor results following excision became known, the operation was discarded, and the joint treated by local nonoperative measures. The exact lines of treatment varied; the American school, championed by Sayre, believed in Traction; the English school under Thomas pinned their faith to Fixation. Then attention was directed to the fact that tuberculosis was a disease affecting the whole of the body, and that the joint condition was a local manifestation of a general condition; and open-air treatment, heliotherapy, and vaccines were brought to the aid of the surgeon. At the present time the popular method of treatment in England is non-operative local treatment (recumbency, traction, and fixation) combined with general treatment (open air, hygiene and heliotherapy). This line of treatment is described in detail in this paper."

He emphasizes that the end-results are not represented by the condition at the time of discharge from the hospital but by the condition years later, after the joint has had to stand the wear and tear of normal life. He further emphasizes that the exact location of the disease in the hip joint is an important factor in determining the end-results. Disease of the acetabulum differs radically from the disease of the head of the femur and this again from synovial disease or disease affecting the neck of the femur.

Fortschritte der Heilstoffchemie (Advance in the Chemistry of Therapeutic Substances)†

THIS is the first of a series of nine volumes on the literature of physiologically active substances. The work will be divided into two parts; part one will cover the patents which have been taken out on such substances, and part two the scientific literature. This is the first of six volumes on the patents and covers the German patents from 1877 to 1900. It is very well arranged so that it is easy to find any patent or any substance desired. In the first 84 pages the patents are arranged according to the classes and groups of the German patent office. This brings together all the patents on any particular subject. A short statement is made concerning the content and purpose of each patent and at the end of each group is a longer statement about the chemistry and the physiologic activity of the members of the group.

In the following 886 pages which make up the body of the book the patents are arranged in numerical order and the texts of the patents are given in full, together with the chemical formulas, drawings of apparatus, etc. Then follows an index of the patentees and a very complete subject index which includes many of the trade names of the patented substances.

It is obvious that the volume contains a mine of useful information conveniently arranged.

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*The Diagnosis, Treatment and End-Results of Tuberculous Disease of the Hip Joint. By George Perkins, M.Ch. (Oxon.), F.R.C.S., Eng. Assistant Surgeon to the Royal National Orthopedic Hospital. Assistant Surgeon to Pyrford Orthopedic Hospital, Orthopedic Registrar, St. Thomas Hospital. The Robert Jones Prize Monograph 1924 published under the auspices of the British Orthopedic Association. Cloth. Price $1.75. Illustrated. Pp. 118. Oxford Univ. Press, 1926.

†Fortschritte der Heilstoffchemie (Advance in the Chemistry of Therapeutic Substances). By J. Houben, Professor of Chemistry in the University of Berlin, Part I, German patents, Walter de Gruter and Co., Berlin, 1926, 80 marks.

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EDITORIALS

Sclerosis of the Pulmonary Artery

SO INFREQUENT is pronounced sclerosis of the pulmonary artery that for a time it was thought that sclerosis was an affection of the greater circulation only. Andral in 1829 first described atheromatous, fibroid or cartilaginous plaques in the pulmonary artery. Bouillaud in 1839 found similar changes in a young child with mitral stenosis. Since then the coincidence of pulmonary arteritis and mitral stenosis has been repeatedly remarked and has been explained as a result of increased tension in the lesser circulation caused by ventricular hypertrophy. Dittrich (1850), Bamberger (1857), Traube (1878) likewise described pulmonary arteritis with coincident mitral stenosis.

Others later found the lesion without accompanying gross cardiac pathology. Then, naturally, the infection-intoxication hypothesis was proposed. Sanne (1877) found the site of predilection at the arterial bifurcations and

attributed the changes to gout, rheumatism, alcoholism, and, as formerly, to hypertension associated with mitral stenosis.

Romberg (1891) proposed three causes for the condition; mitral stenosis, pulmonary tuberculosis, and endocarditis of the pulmonary valve with spread into the lesser circulation. From then until 1910 little advance was made. Giroux in this year reviewed the literature and concluded that pulmonary sclerosis is nearly always secondary to chronic pulmonary infections such as tuberculosis and emphysema or to cardiac pathology, especially mitral stenosis. He also suggested the possibility of a pulmonary arteritis without other etiologic disease. While Romberg did not include primary arteritis in his classification he did describe a case in which no other recognizable cause was found.

Until 1910 the disease was considered as practically always secondary to chronic pathologic processes elsewhere in the body, a terminal condition of only incidental interest and of little importance either from the therapeutic or the diagnostic viewpoint. Here the case would have rested had it not been for the recognition of increasing numbers with sclerosis without other recognizable cause, apparently a primary condition. Such cases were mentioned incidentally by Romberg (1891), by Aust (1892), by Giroux (1910). In 1908 Rogers described ten cases of primary atheroma of the pulmonary artery which he had studied in the Bengal. These he attributed to syphilis. Other workers have since described similar cases and in 1922 Mattirolo, reviewing the literature, found records of nineteen.

This being the case, sclerosis of the pulmonary artery is no longer merely a late manifestation of some other disease but it becomes a primary condition and deserving of individual attention.

The symptoms of the disease are characteristic, consisting of cyanosis and a progressive dyspnea on exertion. The cyanosis becomes so marked that some authors have suggested "black cardiacs" as an appropriate name for the victims of this condition. This would be acceptable if all cases showed associated cardiac pathology but such is not true.

The clinical history of those cases in which the sclerosis is consecutive to valvular disease shows a relatively rapid development, in individuals previously little discommoded, of a steadily increasing dyspnea. Breathlessness exists not only on exertion but also at rest. Shortly the mucous membranes show beginning cyanosis which steadily deepens and spreads to include the skin, the nails and the eyes as in a congenital cyanosis. Exacerbations of dyspnea are not infrequently accompanied by hemoptysis. The lungs fill with râles and death occurs after several months from asphyxia or an intercurrent affection. At autopsy we find a generalized sclerosis of the pulmonary arteries with scattered plaques of atheroma, and not infrequently thrombosis and infarct of the lung. The picture in the pulmonary arteries far outbalances other necropsy findings in the circulatory system. In the heart there is almost invariably a pronounced mitral stenosis.

When the disease follows chronic long-standing pulmonary infections, the early symptoms are rather different. There is no evidence of cardiac disease either subjective or objective. Here we are dealing with persons who

for years have had chronic recurrences of bronchitis, with exacerbations and resulting pulmonary emphysema. Often the provocative cause is a chronic fibroid phthisis. Eventually, however, the dyspnea which has previously existed only with the acute attacks, becomes permanent and this, as in the cardiac cases, is followed by progressing cyanosis. Only later do symptoms of congestive heart failure become manifest.

The postmortem picture in sclerosis consecutive to pulmonary infection, while closely resembling that following a long-standing mitral stenosis, is likely to show a more patchy distribution.

In both cases the heart shows distinct thickening of the right ventricular wall, often greater than the thickness of the left. During life roentgen examination shows an increase in the transverse diameter of the heart, particularly toward the right, an increased pulmonary arborization, with exaggeration of the hilus shadows, and pronounced visibility of the arborization and ramifications of the pulmonary vessels.

While sclerosis is the dominant feature following mitral stenosis and has been attributed to long-continued hypertension in the lesser circulation, the type which is dependent on chronic pulmonary inflammatory processes appears to be more of a true arteritis, the vessel walls showing inflammatory foci, thromboses, even mural vegetations. The scattered distribution of these lesions indicates a subacute pulmonary arteritis, progressing toward generalized sclerosis.

Vaquez insists, however, that the fundamental cause is the same in both. He recognized the predisposing effect of hypertension but believes that in the cardiac cases also, infection is the ultimate cause of the sclerosis, infection more easily acquired in a vessel impaired by long-standing hypertension. He believes that the occasional attacks of hemoptysis are associated with atheromatous plaques.

Of chief interest are the cases of primary or idiopathic sclerosis. Vaquez describes two such cases, one of which was correctly diagnosed radiographically during life. Only three cases are on record in which the diagnosis was established before the death of the patient. The clinical history is as described above but none of the predisposing causes are present. There is no cardiac disease and the lungs are clear of all forms of infection. As we have stated above, Rogers believed that syphilis was the cause of those cases reported by him. Arrillago, whose recent book on pulmonary arteritis is reviewed in this number of the Journal, likewise believes that syphilis is a most important factor. Vaquez noted some improvement in his case following antisyphilitic treatment, but the blood Wassermann was negative and the patient gave no history of venereal disease. Thus while the spirochete is still under suspicion, it has not as yet been found guilty.

Idiopathic pulmonary arteritis has been reported chiefly in young individuals ranging from twelve to forty-seven years. There is usually an increase in the red cell count. Not infrequently anginoid symptoms follow exertion.

Diagnosis is established on radioscopic examination which shows dilation of the pulmonary artery at its origin, sometimes so pronounced that it may

be double the diameter of the aorta; increased size of the heart shadow to the right; arborization shadows extending out into the lung parenchyma.

The pathology in primary arteritis consists of a generalized sclerosis extending into the smallest arteries, which are at times obliterated, with dilation of the main arterial trunk and cardiac alterations as described above. Arteritis and thrombus formation are found especially in the large and medium-size vessels. The systemic circulation shows no evidence of sclerosis.

While Warthin has established that spirochetes may exist in the walls of the pulmonary arteries and Elizalde and Arrillaga found them in a case of pulmonary arteritis complicated by syphilitic bronchopneumonia, Vaquez concludes that the evidence is insufficient and cannot be accepted as final and that while syphilis may be a factor, the cause of idiopathic sclerosis of the pulmonary artery is still obscure.*

REFERENCES

Vaquez, H.: Sclerose de l'artere pulmonaire, Paris Medical, July 3, 1926, xvi, 15.
Arrillaga, F. C.: La Arteritis Pulmonar y suyo Cuadro Clinico, Buenos Aires, 1926.

—*W. T. V.*

The Reviews

OF what use are book reviews? Of what value may they be? Perhaps the least useful purpose to which a review may be put, is as a critical investigation, with the idea of pointing out errors and fallacies (usually unimportant ones), to the apparent aggrandizement of the reviewer.

The reader of a review is, first, interested to know the contents of the book under consideration so that he may decide whether to invest therein. The title is on a subject in which Dr. Jones has been rather interested. How closely does the volume follow the indications of the title? Is the treatment elementary, a textbook discussion, or monographic? Has the author written his text for the benefit of the novitiate or is it highly technical, for the perusal of those whose thoughts and studies have followed similar channels? How well will it fulfil Dr. Jones' requirements?

The printing of book reviews is rather costly and the space devoted thereto is sorely needed. The reviews must therefore justify their existence. To justify their existence, they must be read. To be read they must present to the reader some item or items of information, previously not known by him, —knowledge which he is glad to have for future use.

In so far as practicable the book review section will present to the reader (a) interesting knowledge on the subject under discussion, culled from the volume reviewed, and (b) description of the contents so that the reader may judge as to his personal need for the volume.

We trust that the scientific information printed in these pages will make the reading thereof desirable per se and will thereby justify the space allotted thereto. —*W. T. V.*

*Further discussion of the clinical symptomatology of this condition (Arrillaga) will be found in the book review section of this Journal.